EARLY THERAPEUTIC SUCCESS IN HUNTINGTON'S CHOREA

with a commentary on

A LOCALISED COMMUNITY IN THE HIGHLANDS OF SCOTLAND

By RAE LLEWELYN LYON

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RAE LLEWELYN LYON.

"The phoenix, Hope, can wing her flight
Through the vast deserts of the skies,
And still defying fortune's spite,
Revive and from her ashes rise."

- Cervantes.

Lack of insight often allows patients with Huntington's Chorea to escape from that mental anguish which might be expected if they could foresee their future. Life would be intolerable if they realised that a comparatively early death offered the only release from years of progressive chorea during which they would slowly develop a dementia and probably a psychosis. The suffering often falls instead to the families who are responsible for the care of these pathetic and distressing patients.

The hereditary nature of the disease intensifies the burden of anxiety for blood relations who must often wonder if they will develop the condition themselves or if they will pass it on to their children, which is worse.

Two responsibilities lie heavily on the medical advisors who find such a community in their midst: firstly, the accuracy of diagnosis necessary for the correct application of eugenics requires very painstaking scrutiny of family histories to establish the lines of inheritance which may be halted or on the other hand to remove a burden from the shoulders of the families which are proved to be untainted. Secondly, in treatment, endeavour must continue on a basis of prevention, cure and symptomatic relief. Any measure of success being a seed of hope in such a malady, where the prognosis is always regarded as hopeless and treatment of no avail.

The ensuing pages will demonstrate how these problems have been met in Ross-shire and will indicate the shape of the therapeutic seed which may flourish in the fertile future of medical advance and bloom into a real and permanent cure.

Huntington's Chorea has been defined by Russell Brain (1) as a hereditary disorder characterized pathologically by degeneration of the ganglion cells of the fore-brain and corpus striatum, and clinically by choreiform movements and progressive dementia, which usually begins in early middle life. The course is said to be progressive, terminating in death. No form of treatment is offered other than institutional care. I propose to show in this paper a marked improvement in such sufferers, sufficient in many instances to prevent the need for certification.

HISTORICAL INTRODUCTION

For a little over an hundred years now this syndrome has been recognised. It was first described by C. O. Waters in 1842 (2) and later in 1863 by I. W. Lyon (3) and though the original accounts have apparently been lost they have been quoted by Sinkler (4) who accepts the accuracy of diagnosis.

The name of this disorder derives from George Huntington, the third generation of a family to practise medicine at Easthampton, Long Island.

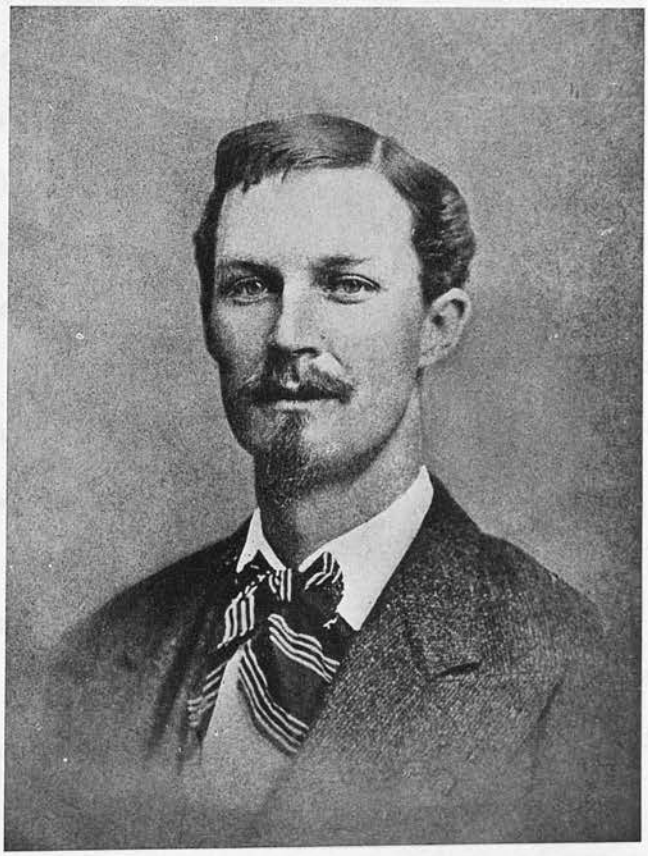


Figure 1. George Huntington.

As Osler (5) remarks, when Huntington called attention to an "Hereditary Chorea" the paper (6) appeared "as an appendix to an everyday sort of paper on Chorea Minor." Nevertheless, this author's name has been associated with the condition ever since and though the description has been more fully explored and expanded, his criteria has been unaltered.

"1. Its hereditary nature."

"2. A tendency to insanity and suicide."

"3. Its manifestation as a grave disease only in adult life."

Of the chorea itself he says "It begins ... by the irregular and spasmodic action of certain muscles. These movements gradually increase ... until every muscle in the body becomes affected." Huntington recognised that "it is confined to certain and fortunately a few families, and has been transmitted to them, an heirloom from generations away back in the dim past." He believed it to be "more common among man than women."

"Of its hereditary nature - when a patient shows manifestation of the disease ... especially if of a serious nature ... the offspring almost invariably suffer. But if these children go through life without it, the thread is broken and the grandchildren ... are free from the disease."

"As the disease progresses the mind becomes ... impaired. The tendency ... to that form of insanity which leads to suicide is marked."

"I have never known a recovery ... but surely increasing by degrees ... until the hapless sufferer is but a quivering wreck of his former self."

"No treatment seems to be of any avail."

Over the years many papers have appeared on the subject and while differing types have been described the characters of the average case has crystallised.

Chorea is commonly the presenting feature, starting insidiously in the upper limbs before spreading to involve face and then lower limbs. The movements are jerky, purposeless, fairly extensive and often repetative which may be described as 'squirming,' 'snaking' or 'weaving.' The consequent inco-ordination starts as a clumsiness of the hands then a liability to drop things. Later symptoms include dysarthria and an unsteady gait. As the condition progresses these involuntary movements increase and become more troublesome until the patient is unable to feed or dress himself and he is exhausted from the continual activity.

The mental disorder may vary greatly. In most cases there is progressive dementia, the patient gradually becoming apathetic and inert. If a psychosis is present it may take any of the many forms which have been described, subtle or overt. Though suicide is often mentioned by American writers, Brain (1) specifically says that it is uncommon.

When the family trait is known a pre-Huntingtonian stage may sometimes be recognised. The chorea starts merely as a fidgeting while the dementia may present as an irritability and loss of memory or as a change in habit by a normally tidy person.

Differing bio-types have been described in different families. The chorea may precede the dementia or the syndrome may present with dementia, Either of these symptoms may be apparently absent. One particular psychosis may keep reappearing throughout one branch of the family.

PATHOLOGY

Several excellent accounts of the morbid anatomy in Huntington's Chorea have been published but it is not proposed to enter into all the various arguments surrounding them as histological studies have not been possible in our cases. The findings are conveniently summarised by McMenemey (22) and are worth attention for the under-:standing they give of the alterations in physiology of these cases.

Cerebral cortex - a moderate degree of gyral atrophy especially in the frontal lobes.

Ventricles - show a degree of dilatation, particularly of the anterior horns when there is marked focal atrophy of the caudate nuclei.

Basal ganglia - A primary loss of nerve cells is to be found particularly in the middle and posterior parts of the putamen and in the caudate nucleus while the anterior quarter of the putamen along with the head of the caudate are not so seriously involved. Though the smaller cells are usually affected, the large cells which may be more resistant are only affected when the disease is well advanced. No cell changes usually occur in the globus pallidus, or in the red nucleus and substantia nigra.

AETIOLOGY

Both sexes are affected and pass the disease on with equal frequency. The disorder is believed to be transmitted by a single dominant gene, so that children of an affected parent may have a 50% chance of inheriting it. There was doubt for some years about the possibility of the disorder to miss a generation but there is now general agreement with Huntington that if the child of a disordered person escapes then the disease will not usually return to that child's descendants.

Age of onset tends to vary even in the same family. Anticipation is an interesting phenomenon where the disease appears to start at a younger age in succeeding generations. This obviously cannot be the rule, however, as it would soon die out. Davenport (7) has discounted this phenomenon with factual proof.

Incidence is exceptionally difficult to determine with accuracy especially in this country as it is present in localised areas rather than being distributed evenly. The modern migration of families may obscure the hereditary nature of the disorder. Several figures have been given for different areas, and these show a surprising correlation.

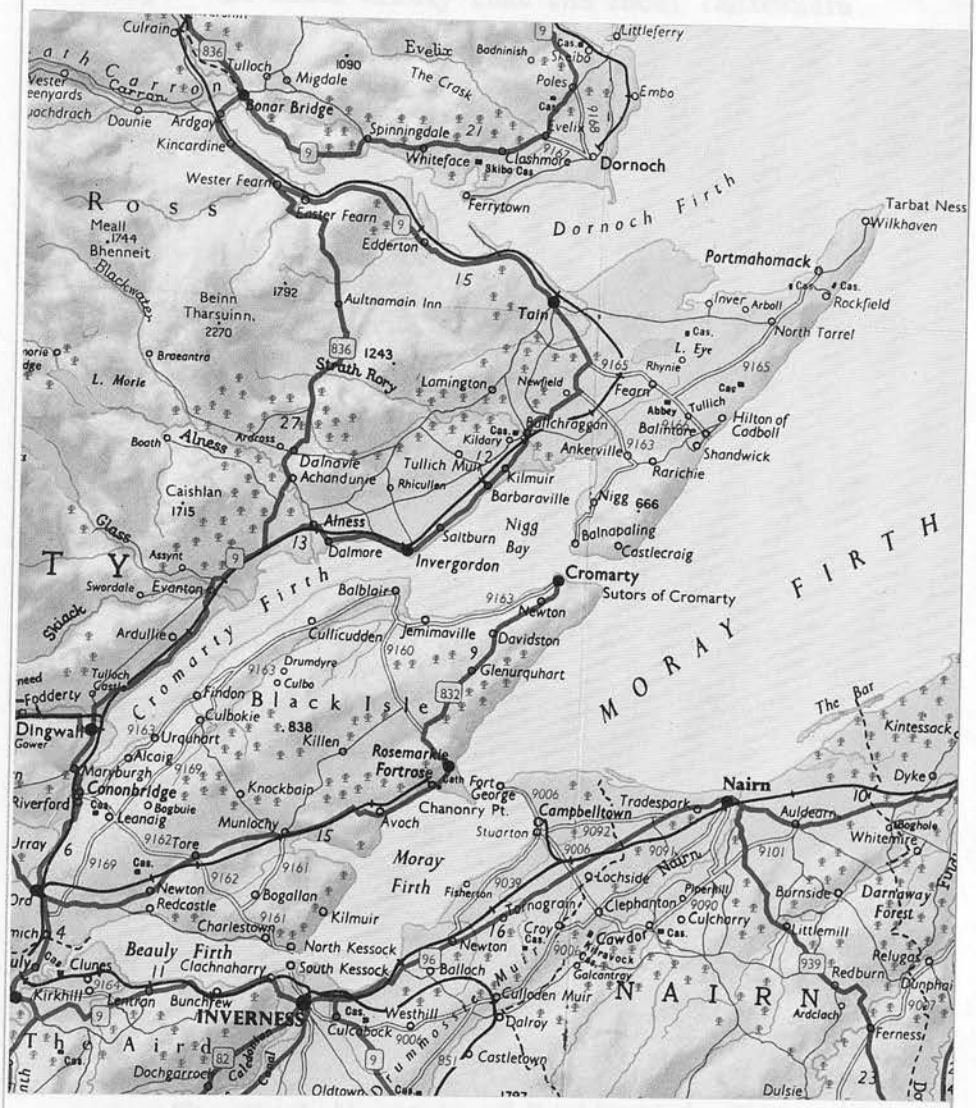
Area	Incidence/100,000	Author.	Year.
Cornwall	5.57	Bickford(8)	1953
Northampton	Less than 5	Plydell (9)	1954
U.S.A.	5.4	Lazarte (10)	1955

TABLE I :- Incidence of Huntington's Chorea.

For similar reasons, distribution of cases in the United Kingdom cannot be precisely known. MacDonald Critchley (11) obtained figures which illustrated a wide scatter throughout England and Wales. The first cases to be described in this country under the title of Huntington's disease were a family at Stoke-on-Trent (12) in 1887. By the end of the nineteenth century the condition had been demonstrated in many scattered places (13-15) including Birmingham (16), London (17), Manchester (18), Bristol (19) and Leith (20). Localised collections of cases have been described more recently in Cornwall (8) and Northampton (9). Huntington's Chorea appears to occur all over the world. It has been claimed, however, (21) that in Europe there is a greater incidence in the southern countries than is to be found among the Scandinavian races, a point of significance when we come to trace its arrival in Scotland.

OCCURRENCE IN ROSS-SHIRE

It has been recognised for some years that Huntington's Chorea is common in the Moray Firth area amongst farming and especially the fishing families. The point of focus which has the highest incidence and the place from where all the families originate is Avoch, a small fishing village in Ross-shire on the south coast of the Black Isle.



Map - Showing Avoch and Moray Firth area.

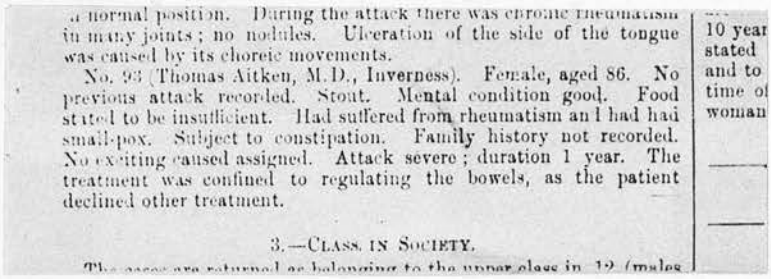
Scale:- 6 miles to 1 inch.

Mentioning the surnames - Patience and MacLeman, MacWilliam (31) has already drawn attention to this but only to point out the presence of the disease in this area and to ponder its source.

Historical evidence about the origin of the village of Avoch and its people is extremely weak. There has long been a settlement there, the nearest habitable area to Ormond Castle, one of the strongholds of the Earls of Moray.

of Moray. It seems likely that the local landowners brought men from the south to improve the fishing between 1690 and 1727 but no direct proof has been discovered to suggest from which part of the country they came.

The earliest published account of Huntington's Chorea in the Highlands may well be this one which was submitted by the first Physician Superintendent of the Inverness and District Asylum (Craig Dunain Hospital) to the Collective Investigation Committee of the British Medical Association (33) which sat from 1882 to 1885.



a normal position. During the attack there was chronic rheumatism in many joints; no nodules. Ulceration of the side of the tongue was caused by its choreic movements.

No. 93 (Thomas Aitken, M.D., Inverness). Female, aged 86. No previous attack recorded. Stout. Mental condition good. Food stated to be insufficient. Had suffered from rheumatism and had had small-pox. Subject to constipation. Family history not recorded. No exciting caused assigned. Attack severe; duration 1 year. The treatment was confined to regulating the bowels, as the patient declined other treatment.

3.—CLASS IN SOCIETY.

The cases are returned as belonging to the upper class in 12 (males

10 year stated and to time of woman

Figure 3. Extract from Brit. Med. J. 26 Feb. 1887. p.426.

The first diagnosis of Huntington's Chorea in these parts appears in a hospital record in 1904 (P.II.3). Thereafter the diagnosis was lost until 1927 when it appeared on the death certificate of P.III.6. At other times it was thought (32) that the patients were demonstrating the late results of chronic alcoholism which was relatively common in the north and the diagnosis has been euphemistically entered as seconday dementia.

The genealogical and clinical studies which ensue are drawn from (a) hospital records (b) Parish registrars' records (c) old parish records (d) local practitioners' medical records and (e) personal memories.

Only/

Only facts which can be verified are detailed. Many difficulties have restricted the completeness of this summary and some are worth mentioning:-

(a) The inhabitants of Avoch have a great dislike and mistrust of strangers.

(b) With only three common surnames amongst the fishermen, there are many families of the same name and differentiation is by means of by-names which may be for the individual or for the family.

(c) It is not permitted for an outsider to learn or use these names and as many describe personal peculiarities it is insulting to use these by-names to an individual.

(d) As this has been a closed community until quite recently, there is considerable in-:breeding which complicates the unravelling of family trees and has led to increased incidence of mental deficiency.

(e) This has caused some of my informants to show a confusion amongst Huntington's Chorea, other psychoses and mental deficiency.

(f) There is a particular reluctance to discuss "the trouble" with strangers.

(g) The patients with established diagnosis have lack of insight and their relatives will often deny even to other villagers that anything is wrong.

(h)/

(h) When old people become frail they may be shut indoors, perhaps actually confined to bed with the result that even the neighbours will be unable to describe the patient's latter years.

(i) Death at Child-birth, death at sea and tuberculosis has taken a heavy toll of the fishermen and their families so that many have died before reaching an age when they might have been expected to develop Huntington's Chorea. It is not uncommon to find individuals who have been married two, three or four times.

(j) Emigration has deprived us of knowledge of some recent generations.

(k) The correct diagnosis was not established until 1904 and lost again until 1927.

(l) The old parish registers (1727-1855) do not give the cause of death.

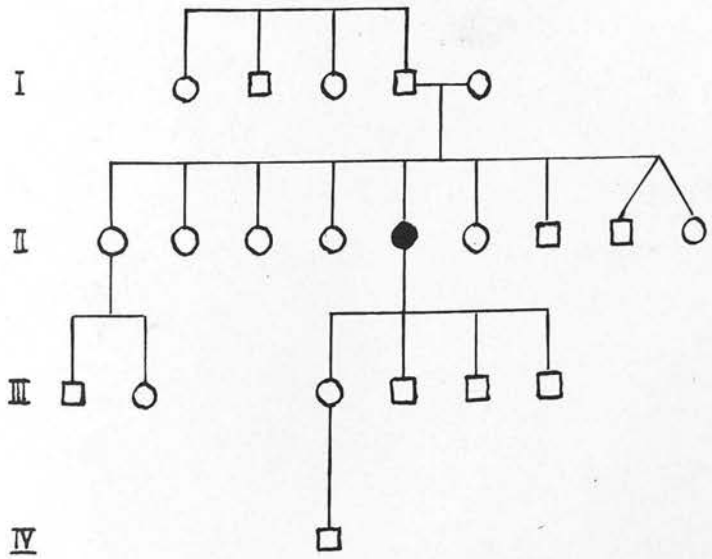
Within the limits of these reservations, the following family trees and personal details are presented:-

FAMILIES A AND B.

The first two patients to be described fall into a special category in that they do not meet all the criteria of Huntington's Chorea. In these instances it has been impossible to trace other members of their families who are afflicted with the disease though as individuals the patients bear many similarities to proved cases.

Case A.II.5 has surviving children who must be watched over many years before the hereditary element can be proved beyond all doubt. No such opportunity for proof is available in case B.III.3.

FAMILY A



KEY

□ = MALE
○ = FEMALE
■ ● = AFFECTED

A.II.5. Born 1900.

Heredity:- This patient is of pure Highland stock, her forebears being small farmers at Sleastry, Bonar Bridge. It was originally recorded that one uncle and a sister had a "shake" but, on review, people who remember the former have described to me a typical picture of Parkinsonian tremor. The case of the sister appears next. Both of the parents died of tuberculosis while the family was young. Of the six other siblings none is suspected of having had a chorea. All four grandparents are remembered and are apparently free of extrapyramidal symptoms.

History:- After their mother died in 1907 and their father died four years later this family were brought up by the maternal grandmother. This girl had a normal country upbringing, marrying a farm servant in 1922. From her nine pregnancies she has now only four living children aged 45, 43, 30 and 21. Two children died of tuberculosis in their early teens. About 1945 the patient found a tendency to nervousness starting, but at this time it was only brought out when she was excited "in company." Three years later, at the age of 48, a "fidgeting" of the right hand began and has slowly progressed and spread to involve all the limbs. Assessment of the case in hospital was undertaken in 1950. She was noted at that time to be rather emotional and with constant coarse jerking movements of the arms, face and head. A very spastic right leg was observed to be causing a shuffling gait. During her two months spell in the ward, some improvement was noted and attributed to the use of Phenobarbitone, 60 mgm. b.d. and diethazine hydrochloride which was slowly built up to

a/

a dose of 1 G. daily.

In the following years the family moved several times and regular medical supervision was lost. For the purpose of this review an unannounced visit was paid initially to her at home. Both her personal appearance and the house showed signs of moderate neglect. A moderate chorea was more obvious in the arms than the legs, where she could disguise it. Trying to fix her hands could not hide their jerkiness. Her head often jerked and the tongue and mouth muscles were also involved. A very slight increase of tone was present in her limbs and there was a similar increase in the tendon jerks. The plantar responses were flexor. An electroencephalographic tracing showed a good dominant rhythm with none of the slowing in the frontal area or elsewhere to suggest a degenerate cortex. The record also had a good amplitude.

An initial shyness was soon overcome and the patient again spoke of her liability to be excited in public. In spite of some depression resulting from her physical handicap she was well composed mentally and had an excellent memory for past and recent event.

Since the onset of the condition no psychiatric disturbance has developed, there has been no obvious loss of mental function and, a more important negative observation is that the chorea has not progressed to any marked extent in the last ten years.

She had in the interval been treated very intermittently with Benzhexol Hydrochloride but claimed most benefit from Phenobarbitone.

Comment:- Though previously accepted as a case of Huntington's Chorea this patient has no traceable relatives with a true chorea, neither is she from the usual affected stock. There is no doubt, however, that her condition should be defined as a chorea and before diagnosing a non-hereditary form it is necessary to make one reservation. As salmon fishing has been pursued for many years at Bonar Bridge, it is just possible that a strain has been introduced illicitly by an Avoch fisherman into this Highland stock. This postulation is unlikely in view of the absence of promiscuity in the Avoch folks which will be commented on later.

A.II.1. Born 1894.

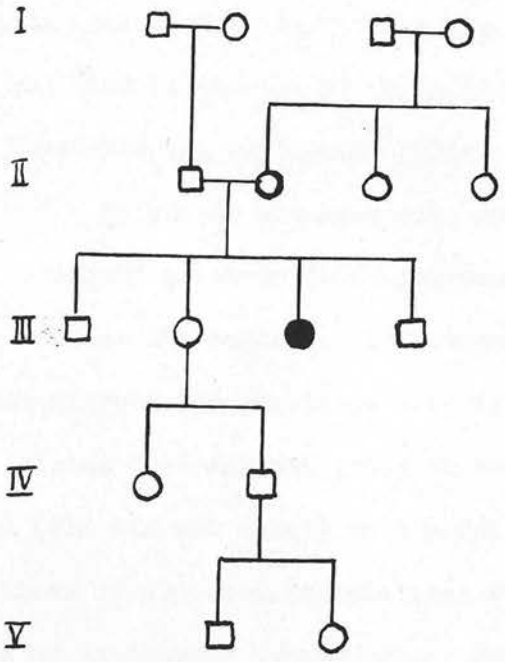
Heredity:- Eldest sister of the above. Daughter has a functional hesitation of speech. Son appears to have a spasmodic torticollis.

History:- In the previous patient's old hospital records this sister was said to have had a shake. She was therefore examined in her home. The house was rather above the average for a farm servant, being well kept, clean, tidy and well polished. The patient's person was well cared for and her clothes clean. Her right hand exhibited a fine resting tremor which disappeared on voluntary movement. In addition a superimposed twitch was present and appeared to be quite involuntary. Her husband claims that this was present at the time of their wedding forty years ago. It has commonly been accentuated by excitement but has not progressed. This twitch was a sudden swift jerk in one plane only with immediate return to the original

position after the fashion of a nervous tick and certainly not a chorea. Some slight tremor could be detected in the right foot on scrutiny but the left half of the body was not affected. Speech, intellect and co-ordination were well preserved and the muscles of expression moved briskly in response to humour. No increase in tone or in tendon jerk response was discerned and there were no other neurological abnormalities.

Comment:- The appearance of this patient's jerking right hand in association with the functional disorders in her children suggests a 'tick' superimposed on a very early and, as yet, dubious Parkinsonism. These findings break the diagnosis of Huntington's Chorea in the family and this is in keeping with the conception that the affected strain does not run in the clansfolk in the Highlands.

FAMILY B



B.III.3. Born 1896.

Heredity:- No affection in siblings and no chorea obvious in parents or grandparents.

History:- This girl grew up in a farming family. Her paternal grandparents had been farm servant and house servant on the estate of Rosskeen at the time of the wedding in 1881, her maternal grandfather being a saddler. Over the years the family fortunes can be traced as they became first small-holders in Easter Ross, then small farmers at Gollanfield in Inverness-shire. She spent her early life helping at home, but later moved about taking

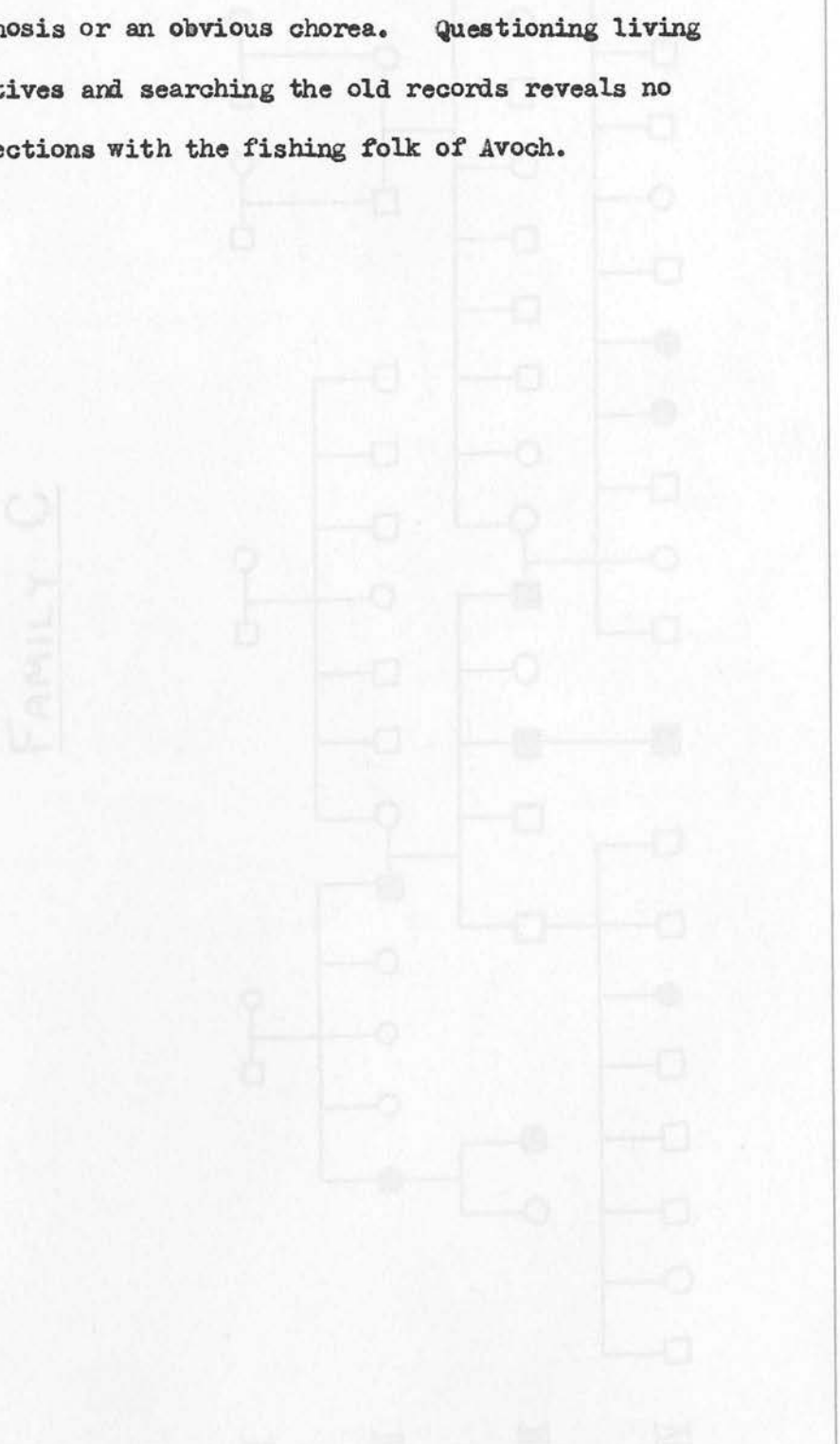
house-keeper's jobs at farms. It is perhaps of significance that she was on the point of becoming engaged to be married but had to return home urgently to nurse (for twelve years) her mother who had suffered a shock. Thereafter the patient looked after her father who was a "fine old man" and who died at the age of 84 in 1937. She returned to the house-keeping employment after his death.

By people who knew her, she is described as being "old maidish" given to "affectations."

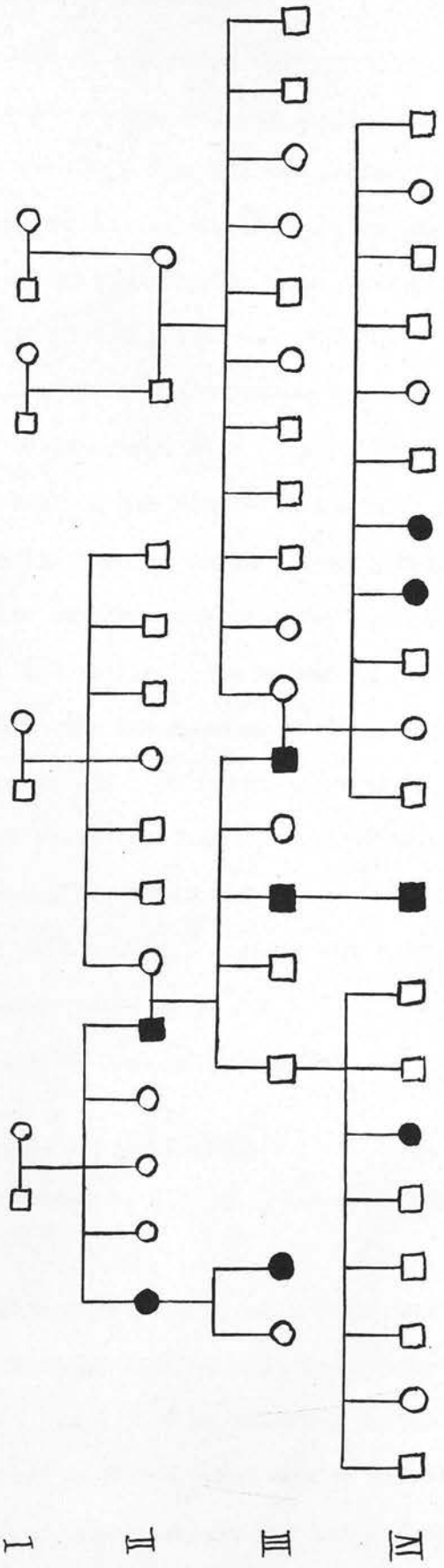
At the beginning of October, 1953, (aet 47) she became nervous and excitable with frequent grimacing and wild claims that she was going to be married to a man called Smith (who did not exist) on the following week. She had delusions of supposed associations with this man. The state of excitement became worse, she became confused and was admitted to Craig Dunain Hospital on 30th October. The diagnosis at this time was of an acute confusional state. Examination showed a fine tremor and slightly erratic co-ordination. She was confused and excitable. At times she grimaced and laughed inanely, suddenly sitting up in bed gasticulating. After a week in hospital it was noted that she was settling mentally, was not quite so unstable and was able to be up each day. Two months later, jerking choreiform movements and staccato speech were observed. Her physical condition deteriorated slowly and she died on 13th December, 1949. Cause of death was entered as Huntington's Chorea.

Comment:- Though there is no doubt that chorea developed in this case, the sex-association at the commencement of her psychosis is unusual in this country.

Her father certainly had no stigmata of Huntington's Chorea and neither had her mother who was remembered by the patient's niece as being cross, with thick speech and a right-sided hemiplegia but lacking either an overt psychosis or an obvious chorea. Questioning living relatives and searching the old records reveals no connections with the fishing folk of Avoch.



FAMILY C



C.II.5. Born 1844.

Heredity:- It is not known whether this man's parents had Huntington's Chorea but the supposition is that his mother may have been the one who passed it on. The patient's sister and many of his issue were afflicted.

History:- There was considerable poverty in the village when this patient was a lad and this was intensified for the family when the father was drowned when this child was only eleven years old. Up till the age of twenty-one he never went to sea himself but worked as a cattleherd above Beauly. Later on he became a fisherman and in his more mature days was renowned for his skill and indifference to risk and danger. He worked on solidly all his life, only passing over the command of the fishing boat to his son at the age of 65. He never exhibited a psychiatric upset but about the time he retired the chorea started. In this case, the shake was almost entirely confined to the head with nodding, shaking and grimacing. He survived a bare three years more.

Comment:- A mild case of late onset.

C.II.1. Born 1835.

Heredity:- Sister of C.II.5. Daughter was affected also.

History:- This patient married a fisherman and had two daughters. Her husband died in 1895 and she retired to bed for the next three years. When admitted to the mental hospital in 1898 she had an established chorea as well as delusions of persecution, the constant cry being that she was being maltreated and not being given adequate food.

On admission she looked older than her years. She was restless, excitable, incoherent and with a complete disregard for her cleanliness. Whilst still in the Waiting Room she had a syncopal attack and very nearly died. A year later it was noted that she was "still crying for whisky" and "not looking the better for her very adequate food."

During her second year in hospital she began to fail noticeably and the choreiform movements became worse. After her death in the following year her certificate gave the cause as:-

Chronic cerebral disease)
Chorea) Several years.
Faulty heart)

A post-mortem examination was carried out but the report has been lost.

Comment:- Huntington's Chorea seems to have started fairly late in life. It was complicated latterly by dementia. At the time of removal to hospital she had delusions of persecution as well as a presumed chronic alcoholism.

C.III.2 Born 1868.

Heredity:- Daughter of the above C.II.1.

History:- After her marriage this girl moved to the Invergordon district. Towards the end of the first war she began to develop a shake of the hands and head.

During the five years after it started she became very badly disabled but seemed to retain her faculties well enough to manage at home. In the winter of 1923 she died from exposure in a very severe snowstorm in which she had been lost for three days.

Comment:- The onset here is at an earlier age. Again we see how accidental or sudden death may distort the average survival time in any patient.

C.III.7. Born 1867.

Heredity:- Son of C.II.5.

History:- This man seems to have been of a rather different stamp than is usually found in Avoch. He was spoken of as having had a nervous disposition and it is clear from the anecdotes that he was felt to lack the usual courage found amongst the fisherman. It seems rather that he lacked the ability to take responsibility for, during all the years he was a fisherman, he would never take the wheel of the big boat though he was willing enough to go out alone in his home-made yawl. On one occasion he was unperturbed when a steamer hailed him, alone in a small cockle-shell boat to tell him he was 40 miles out to sea off Fraserburgh.

He was admitted to a mental hospital in 1931 under a certificate which stated - "A man of poor mentality with the appearance and demeanour of an insane person. He suffers from chorea (Huntington's), subject to fits of violent temper." The hospital admission note observes that his recent behaviour had been outrageous. He had been drinking heavily for six years, dull, inclined to brood on things and suspicious of his neighbours. Examination showed a large bruise on his jaw. There were general choreic movements, slurred speech, poor co-ordination, staggering, ataxia and Rhombergism. Plantar reflexes -
He was thought to be enfeebled in mind. W.R. negative.

C.S.F. - Sugar 0.106%; Pandy sl. positive; Gold test 112332100000.

From the record it is clear that after he had recovered from the alcoholism he settled well in the ward.

The progress reports which were written with a touch of affection in their terms indicate a fairly rapid loss of physical and mental ability. After an attack of paratyphoid in 1934 he became very ataxic and quite demented. He survived into 1937, when on 30th January he suddenly collapsed and died about 12 hours later.

Comment:- Chorea and dementia were well marked at the end but alcoholism had confused the earlier picture.

C.III.5. Born 1871.

Heredity:- Son of C.II.5.

History:- This patient was a robust hard-working fisherman until the last two years of his life. He was said to be a very intelligent man but with a liking for drink. At the age of 61 the athetoid movements made their appearance but only advanced a little to involve the arms and head before he died of a cerebral haemorrhage in 1932.

Comment:- The mild case of Huntington's Chorea which is illustrated here would surely have become much worse if he had survived longer.

C.IV.9. Born 1910.

Heredity:- Son of above, C.III.5, second youngest of five boys, the remainder of whom all died in infancy.

History:- Even as a youngster the neighbours always regarded this lad as being simple-minded. When he left school he tended to drift from one labouring job to

another. At the outbreak of the war he volunteered for the Navy but was invalided out in 1940 (without a pension) because of chronic bronchitis. He spent three weeks in a chest hospital in 1957 and since then has been unable to work as "his chest always gives way."

After the patient's wife and father died he tended to neglect himself and his general condition deteriorated markedly. During 1958 he spent six months in Craig Dunain Hospital and improved considerably with regular attention. His memory was good; he had no delusions or hallucinations. He was described as a quite simple-minded type of person who needs looking after. The chorea was widespread but not severe or incapacitating. At the present time he has unfortunately reverted to his former state of neglect. He lives by himself in near primitive conditions, being ill-nourished, ill-clad and ill-mannered.

Examination shows a generalised athetosis of all limbs which interferes markedly with his gait and co-ordination while the writhing neck and grimacing disturbs his speech. The reflexes are brisk and equal. Tone is a little increased.

Comment:- This distressing case illustrates a mixture of simple-mindedness and Huntington's Chorea.

C.IV.6. Born 1911.

Heredity:- The patient's father, a brother of C.III.7 was lost at sea during the First War at the age of 44 without having developed an obvious chorea.

History:- This lady married a policeman and settled in London. Two years ago she revisited Avoch when the

chorea was obvious. It had started at the age of 40 and her husband decided to retire to Bristol with the rank of Inspector (C.I.D.).

Comment:- Though very little is known about this patient, these few details were established as she visited a local doctor during her recent visit.

C.IV.13. Born 1896.

Heredity:- The father, grandfather, a brother and a sister are all well established cases of Huntington's Chorea.

History:- Before she was married this lady worked on the domestic staff of Rosehaugh House. From the days of school she was troubled with an indigestion and anaemia until brought in as an emergency to the Royal Northern Infirmary in 1939 following a haematemesis. This month in hospital seems to have stopped her digestive upsets. In 1945 at the age of 50 the family first noticed that she began nodding her head. A mild, placid soul, she has never exhibited any mental disturbance or the slightest change in her demeanour. The movements which were never strong or very sudden involved the whole body and gradually developed until she found that they could interfere with complicated movements such as putting on her stockings.

Examination showed some slight rigidity and a barely perceptible lack of co-ordination, especially in the arms, in addition to the chorea.

Treatment:- Over the years many drugs have been given to this patient and include Benzhexol Hydrochloride, Chlorpromazine, Reserpine and Tolazoline. Amongst the most useful have been Phenobarbitone and Amylobarbitone.

Comment:- Though Huntington's Chorea is well established in this case, she continues to be ambulant after 15 years. Recent therapeutic attempts have greatly improved her athetosis.

C.IV.14. Born 1893

Heredity:- Daughter of C.III.7 and sister of C.IV.13.

History:- As a girl this patient was a nervous and excitable type of person. On leaving school, she worked as a fish-cleaner until her marriage to a Glasgow railway carter in 1920. At the age of 40 her shake became noticed by the family and, though it spread and became worse, no psychosis developed. She was severely demented before she died in 1945 in Govan General Hospital.

Comment:- This patient survived for 12 years after the onset of Huntington's Chorea at the age of 40.

FAMILY K
I
II
III
IV
V

K.II.2. Born ? 1820.

Heredity:- No antecedents of this lady are known nor can any records of them be found. An unconfirmed story suggests that she may have been a near relation (?sister) of C.I.2.

History:- According to the entry in the register this patient was married on September 22nd, 1842. She is spoken of as a very old lady who died in 1900 when she was probably about 80 years old. As she was choreic for about 15 years she is remembered as a terrifying character by a few old villagers who were then very young.

K.III.8. Born 1862.

Heredity:- Three children and one sister were definitely affected as well as this patient himself.

History:- As a child this patient was very small and he developed a nick-name related to this peculiarity. Later in life he was employed locally at the fishing and was a very tall and strong man. He lived to the age of 80 and developed choreiform movements only during the latter five years. No psychosis seems to have developed even at the end.

Comment:- A strong active man who developed a mild chorea when he was old.

K.III.3. Born 1840.

Heredity:- Sister of K.III.8.

History:- This lady was the wife of a fisherman and followed that busy life for 70 years. Her two sons were mentally defective but they have exhibited no chorea.

For the last 12 years of her life she became slovenly, then unkempt, her house showing signs of neglect. Shortly before going to stay with her daughter-in-law the chorea became obvious in the arms and head but latterly she was very frail and was not allowed out to be seen. She died at the age of 80.

Comment:- A strain of mental defectiveness is present in this family as well as the Huntington's Chorea which developed late in this case.

K.IV.1. Born 1879.

Heredity:- Eldest daughter of K.III.1. The patient's mother came from Buckie and is presumed to be unaffected. The father showed no signs of Huntington's Chorea before he died at the age of 65. The possibilities are (a) that the father would have developed signs if he had survived longer and that he was the carrier, or (b) that the firstborn of a family is occasionally illegitimate.

History:- This patient married a local boy but soon moved to Inverness where he worked as a labourer. He was killed by a blow on the head when working with a dredger and his widow brought up the family on her own. When she was just over 70 years old the chorea made its appearance. Her personal appearance suffered badly as she apparently developed a dementia. One day about five years later she was found dead in the fireplace following what was thought to be a cerebral haemorrhage.

Comment:- The direct inheritance cannot be established in this case but both an uncle and aunt were afflicted.

K.IV.26. Born 1892.

Heredity:- Daughter of K.III.8.

History:- Blithe and always cheerful as a young person even though inclined strongly towards religion, this girl was very popular because of her bright disposition. She married a fisherman and had a family of six. At the age of 48 the athetosis of Huntington's Chorea manifested itself but she never lost her spirits. In 1950 she had a laparotomy for a colonic neoplasm but though the primary was excised it was obvious that lymphatic spread had already occurred. The chorea was very marked at this stage but it steadied a little in the ward when she was settled with Phenobarbitone. Co-ordination was interfered with and the reflexes were a little brisker than normal. Even when she returned home she retained her cheerfulness and her good memory.

Comment:- Onset in a young person but no psychosis or dementia.

K.IV.32 Born 1896.

Heredity:- The patient's father and aunt were sufferers from Huntington's Chorea. From the mother's side the family inherited a streak of mental deficiency. Of the nine siblings, three have chorea and three are defective.

History:- Apart from a tendency to faint while at school this patient enjoyed a perfectly healthy youth. At the age of 14 he started work as a gardener at Rosehaugh House but left this when he was 17 to begin work as a cook on one of the fishing boats. He served at the Dardanelles during the First World War and was later blown up in his

ship off St. Catherine's light. After the war he returned to the fishing and, in the spring-time, worked with the forestry. As a young man he was an irritable and fiery character. Over a spell of about 20 years he indulged in street-corner preaching - full of vehemence and commonly going on for 3-4 hours.

In 1955 he had to stop work after receiving a blow on the head. Soon after this he was noticed to be developing a coarse tremor of the hands. Initially this was only seen after his preaching sessions but gradually it became more constant and over the next year it extended to involve the whole of both arms and then to spread to face, head and legs.

Examination revealed a slight increase of muscle tone associated with symmetrical increase of tendon reflexes as the only abnormality accompanying the chorea. The motions of his body were continual though they could be suppressed slightly and for short times while carrying out a planned movement. Involved were his hands, arms, neck, face, tongue, legs and trunk.

Comment:- An obvious case of Huntington's Chorea complicated or associated with a strong religious trait.

K.V.2. Born 1920.

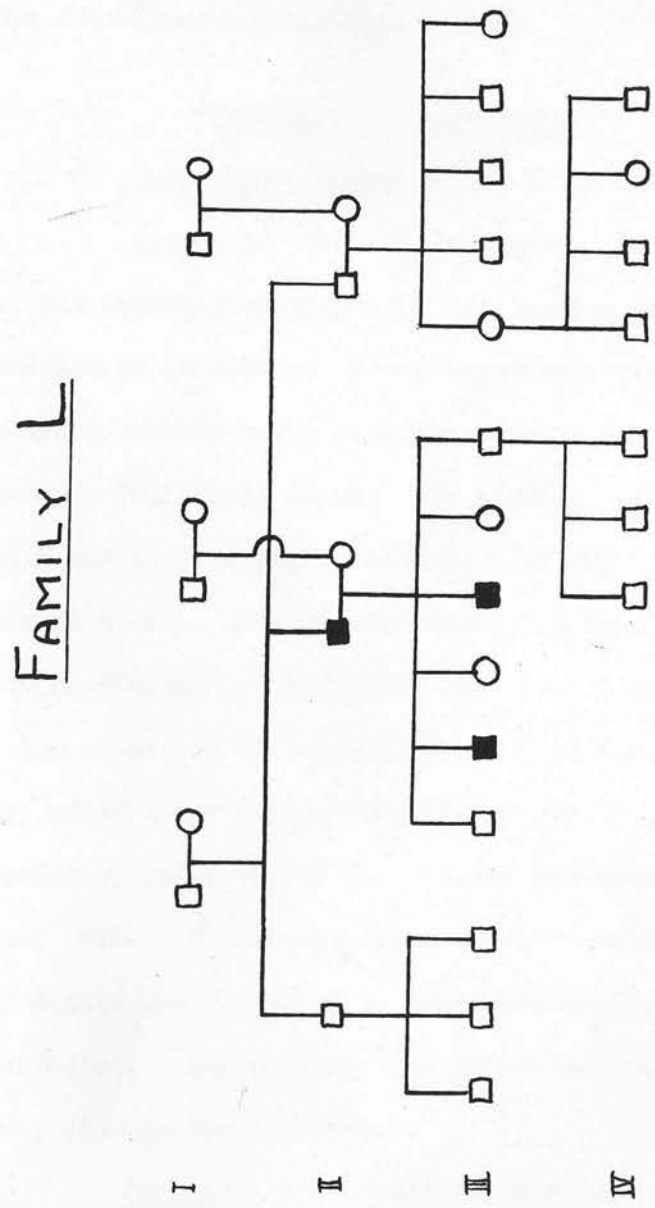
Heredity:- Daughter of K.IV.32.

History:- The second eldest in her family, this girl was spontaneously delivered after a normal pregnancy. She learned to sit up, to walk, to talk and to feed herself at the normal times and was to all observers a perfectly normal child. At school she was only an average pupil -

the only prize she ever took was the one in Scripture. She spent a few years serving in a shop in Inverness after about 15 months working as a domestic servant. At the age of 30 she married a fisherman and settling in Avoch, their first child appeared in the first year of matrimony. While the boy was young, she was frequently up at night and admits that she found it a great worry to look after a baby. She became tired, irritable and fidgety. In 1951 she was pregnant again. It was then obvious that these symptoms were becoming worse and she was in fact showing athetoid movements in her right hand and leg. She was admitted to hospital where the pregnancy was terminated. On closer assessment it was thought that she was a little simple. Involuntary movements were present in the head and neck. No cranial nerve lesions were found. Co-ordination was a little impaired but motor power was not reduced. There was no increase in tone and no signs of spasticity.

During her stay in hospital a mixture was unsuccessfully tried t.i.d. of L-Belladonna 0.1 mgm., Ergometrine Tartrate 0.3 mgm. and Phenobarbitone 20 mgm. Phenobarbitone 60 mgm. t.i.d. was found to help a little. Since that time she has continued at home, gradually finding that a growing child was less of a worry. She has shown a tendency to spells of moodiness when the house tends to be neglected a little but her mother has proved to be a great ally to her.

Comment:- The early diagnosis of Huntington's Chorea was difficult in this case. This patient seems to have a little insight though termination of the pregnancy was probably sought as a prophylaxis.


FAMILY L
I
II
III
IV

FAMILY L.

The namefor L.I.2 appears on the birth certificates of her children but few memories of her remain in the village. It is possible, however, that she was a sister of P.II.12. and that this could be a connection between families L and P.

L.II.2. Born 1860.

Heredity:- Father of two affected males.

History:- This fisherman was mostly remembered for his muscular strength and his drunken sprees. On one occasion he is said to have stepped out from the Bar, felled a runaway horse with his bare fist and returned again to finish his drink. He married a daughter of P.I.5 and it is thought that she also may have been from tainted stock. The chronic alcoholic habits combined with Huntington's Chorea must have been a great strain on the patient's wife who made her children promise that they would never marry, thus indicating that the hereditary character of the disease was considered even about 1870. Of her six children only one disregarded her wishes and so far as is known his family is at present unaffected. The patient died at the age of 40 after being choreic for ten years.

Comment:- A particularly tragic combination of Huntington's Chorea with chronic and acute alcoholism.

L.III.5. Born 1884.

Heredity:- Son of L.II.2.

History:- Trained as a fisherman, this lad joined

the Navy at the age of 30 and served with distinction from the commencement of the First War. In 1917 he started to be fidgety and soon developed chorea. After the war he emigrated to Canada and was drowned while bathing at Vancouver in 1922. It has been suggested that this patient intentionally waded out to sea until he was overcome.

Comment:- If it is true that this man took his own life fearing what the future held for him, he is the only case of suicide in this series.

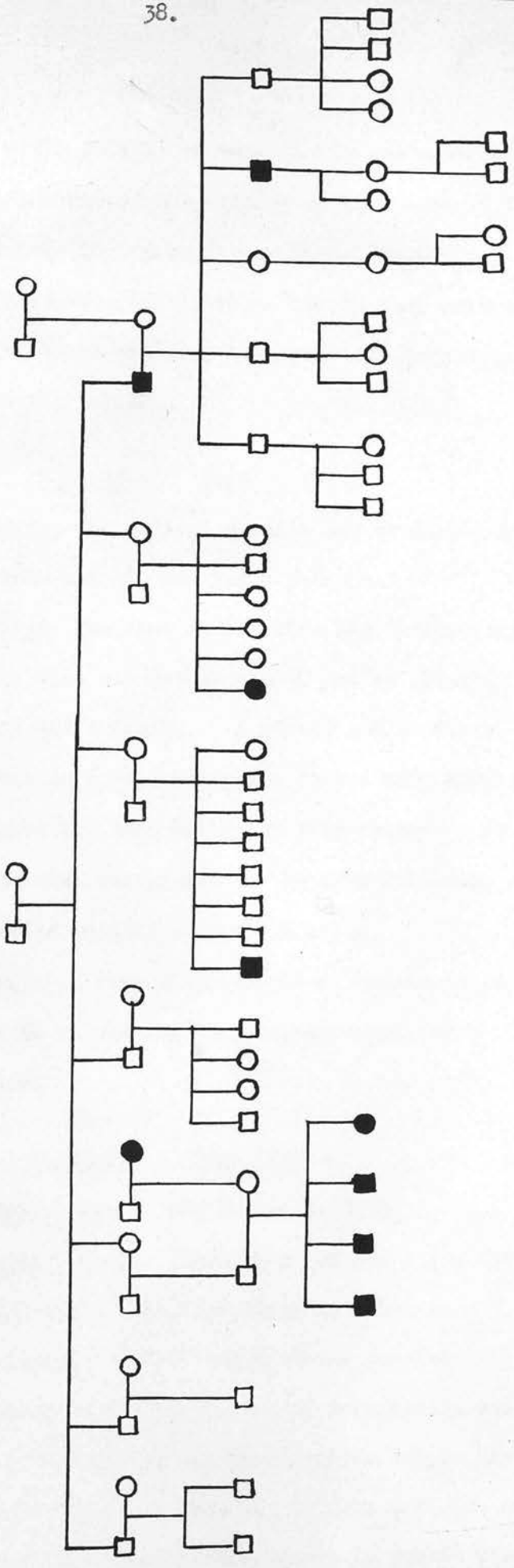
L.III.7 Born 1889.

Heredity:- Brother of the above, L.III.5.

History:- Though this man started life as a fisherman he joined the First Battalion of the Seaforth Highlanders at the outbreak of the Great War and saw action with them on many occasions. His symptoms of Huntington's Chorea started in 1918 and he died at home two years later.

Comment:- The onset of the disease and its duration were curiously similar in these two brothers.

FAMILY N



FAMILY N.

The early details of this family are uncertain because of the absence of the wedding certificates of N.II.15. The date is frequently mentioned in their children's certificates and it seems likely that contrary to the belief of their children this pair may have been married outwith the parish.

N.II.15. Born 1849.

Heredity:- No medical details are available about this man's parents but his son was a patient.

History:- The last member of a big family, this patient was born when his mother was 50 and an older daughter already had a family. A strong and tireless fisherman all his days he developed a chorea only during his last two years and this was never very severe. No Psychosis or dementia was present. He died following a cerebral thrombosis in 1923 at the age of 74.

Comment:- A very mild example of Huntington's Chorea starting in an old man who only survived for a further two years.

N.III.27. Born 1884.

Heredity:- Son of the above, N.II.15.

History:- In his youth this man had a reputation for being intellectual. He appears to have had an impressive knowledge, all self-acquired and possibly acquired to bolster up a mild feeling of inferiority and frustration. He was always deeply religious but in his latter and disturbed years he was apt to make a figure of himself by delivering religious discourses in public places.

All his life he was very emotionally tense.

Two injuries occured to him, the first at the age of 49 when he injured a leg by a fall into a ship's hold. Twentynine years later, as an old man of 68, he was knocked unconscious by a motor bicycle. The symptoms of Huntington's chorea started about the age of 64. The hands, arms, face and legs became involved over the space of a year and he was not only unsteady on his legs but was unable to look after himself or feed himself properly. He died of bronchopneumonia in Craig Dunain Hospital in February, 1959.

Comment:- An example of Huntington's disease starting at the age of retiral with survival for 11 years.

N.III.10. Born 1860.

Heredity:- Nephew of N.II.15. State of mother unknown.

History:- This man left the village at a fairly young age. He joined the Police Force at Dundee where he died aged 75 after having exhibited chorea for only a year.

N.III.18. Born 1863.

Heredity:- Niece of N.II.15. This girl was the eldest of the family and as neither of her parents were afflicted with Huntington's Chorea though they lived to a fair age there is possible doubt in the source of her inheritance.

History:- Again we see a girl from a fishing family working as a domestic then at the fish cleaning before marrying a fisherman. Her symptoms began about the age of 71 but spread very quickly to involve her whole body

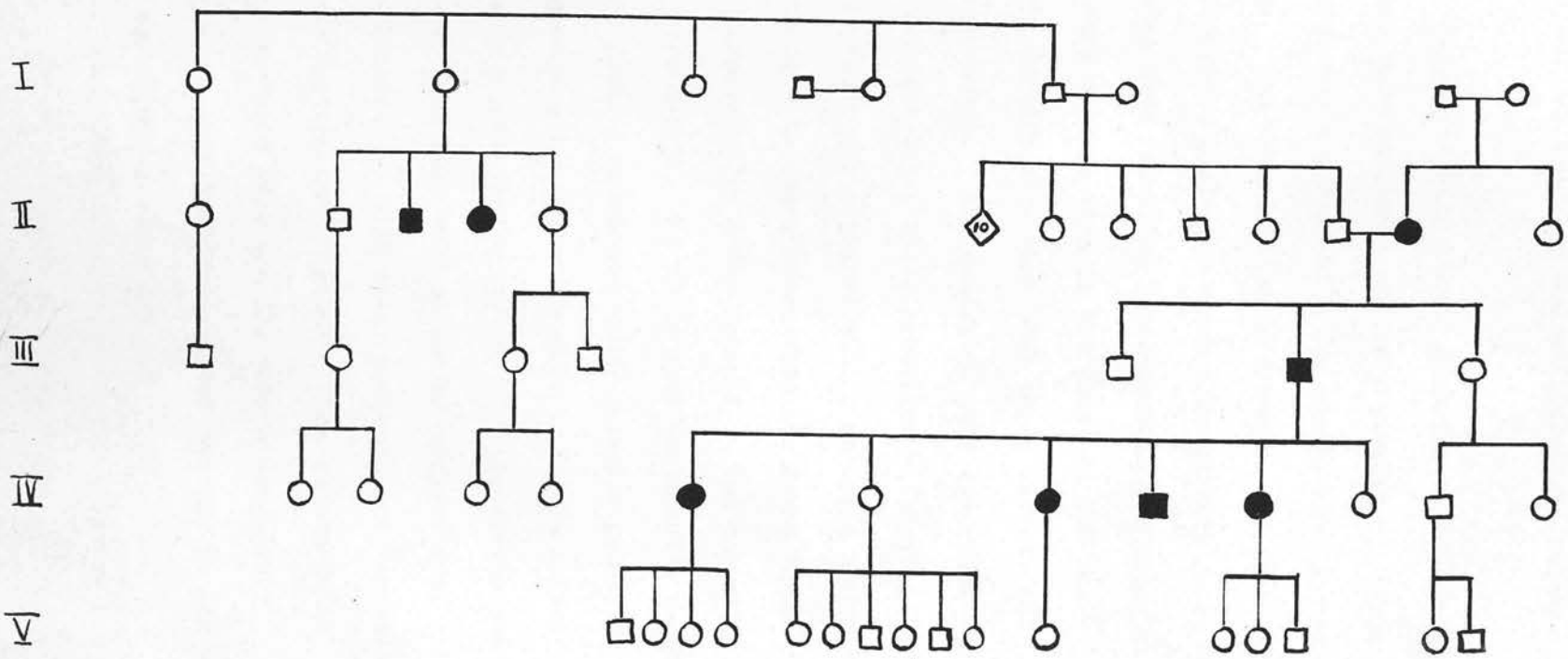
with the continual chorea. In spite of being severely affected, her mentality was not disturbed and the family cared for her at home. At the end, unfortunately, her daughter became pregnant and when her child was to be born the patient was transferred to Craig Dunain Hospital where she died a fortnight later.

Comment:- An unusually severe case for an elderly patient.

N.V.1-4.

The grandparents of this family all apparently originated from Avoch though the connections are not quite clear. It has been suggested that the strain of Huntington's disease was carried by both sides of the family though there is evidence of chorea only in one grandmother (N.II.8). The family history is indeed tragic. A brother of N.III.4 is said to have been stabbed in a brawl on a troop train and the body thrown out of the train at Carlisle. N.III.5 died of pulmonary tubercle at an early age and one of her sisters committed suicide. All four children are at present in mental hospitals suffering from Huntington's Chorea. The local practitioner has kindly supplied information for the statistical analysis.

FAMILY P



P.II.12. Born 1846.

Heredity:- This patient's mother and her husband's mother were half-sisters. By one account which cannot be confirmed, her mother had Huntington's Chorea. Of the patient's sisters, neither was afflicted and neither had issue.

History:- Many people describe this lady as having been very beautiful and very vivacious. This was all changed over a period of a few months when she was 44 years old. She was admitted to a mental asylum in 1892 as a case of chronic mania for which a hereditary cause was suspected as some relatives (described in the notes as cousins) were at that time in the hospital but the Registrar's certificates show that their parents all had different surnames. The admission note describes her as having incoherent talk, silly behaviour - fancying that the local woods where she gathered sticks belonged to her and often fighting with other women whom she found there. She had often threatened to drown herself. The choreiform movements were marked, the whole body continually making unnecessary jerking movements which caused a peculiar staccato speech and a totterihg gait. In the following year there is a note to the effect that the chorea was generalised. She made lewd signs and suggestions, constantly interfering with other patients and "probably suffers from Huntington's Chorea." She became quite demented by the next year and the chorea was slowly exhausting her. She died suddenly of syncope in her chair. Death was certified as being due to:-

Phthisis Pulmonis - several years.

Choreic Exhaustion - 21 days.

Comment:- A case of onset in a young person yet short duration. The suggested diagnosis is the earliest discovered reference to Huntington's Chorea in this neighbourhood.

P.III.6. Born 1869.

Heredity:- The mother of this patient was affected with a shake. Five of his seven children have also developed it. His mother's sister and two sisters of his father are reported to have been in an asylum but this claim cannot be substantiated.

History:- Memories are growing dim about this man and his early life seems to have been that of an average fisherman being always temperate. When he was 44 years old he started to develop a moodiness later becoming dull and depressed with a tendency to brood. Shortly before his admission to Inverness District Asylum at the age of 55 he became dirty in his habits, restless and noisy, and was not sleeping well. His talk was "foolish." The precipitating cause of his admission to hospital was he threatened to do harm to himself and others. At that time he was found to be depressed, slightly confused, enfeebled and childish. He did not see that there "is any reason for him being in hospital as he is not ill." Questions were answered slowly but to the point.

Examination showed an elevated blood pressure and thickened vessels. His tongue had a coarse tremor: reflexes normal and no chorea noticed. The diagnosis made was of secondary dementia. For some time he remained quiet in bed, facile and with grandiose ideas. Some improvement occurred and he was able to go out with

working parties for three years but he was never reliable. An attack of influenza made him much more feeble and his athetoid movements were greatly accentuated. A month later (29.4.27), he died aged 58, the diagnosis carried by the death certificate being Huntington's Chorea.

Comment:- There is some doubt if Huntington's Chorea was recognised in the countryside at the time of his admission to hospital. The chorea probably developed in the patient while he was in hospital. Tracing family connections are necessarily confused here as the patient's father had three, if not four, wives.

P.IV.5. Born 1902.

Heredity:- Daughter of P.III.6.

History:- This patient married a farm worker and bred a family of three girls and a boy who was killed in the war. Her first symptoms were the jerking movements of limbs and head which were first apparent when she was 42 years old. For some years she managed tolook after her house and her family though there was a decline in her standard of cleanliness. Her walking gradually became impaired and when she was 50 (1951) she fell occasionally. Headaches had always been a complaint of hers.

Examination at this time is reported as showing euphoria, slurred speech, grimacing and jerking movements of head, trunk and limbs.

A course of Benzhexol Hydrochloride, 20 mgm. daily had to be abandonned as the headaches were made worse. Ethopropazine Hydrochloride, 50 mgm. q.i.d. and Tolazoline 125 mgm. daily were substituted but she would not continue these on leaving hospital after a month. For two years

she continued at home but was liable to violent outbursts in which the house was slowly but very completely wrecked.

In 1945 (aet 52) she was removed to Craig Dunain Hospital where she was described as being mentally clear, cheerful and happy, getting up every day and later going for walks with assistance. She was able to feed herself but was unable to dress. There were continuous athetoid movements of the whole body. Procaine Ammide 0.25 G. q.i.d. Mephenesin 1 G. and Tolazoline 25 mgm. q.i.d. were each tried in turn but without success and she died after 18 months of a cerebral thrombosis.

Comment:- A typical case showing no real improvement on the various treatments then available.

P.IV.7. Born 1907.

Heredity:- Daughter of P.III.6.

History:- After her marriage this lady settled in Newcastle and knowledge of her was lost until an enquiry came from the psychiatrists in that area. Her daughter was contemplating matrimony and wanted advice as the mother was suffering from Huntington's Chorea.

Comment:- Though it can be taken that this lady is affected, the clinical details are not known precisely and therefore cannot be included in the analysis of results.

P.IV.8. Born,1911.

Heredity:- The father and grandmother of this man were known to have been affected.

History:- After spending a short time at the fishing this patient joined the Merchant Service and was mostly away from home thereafter. He had head injuries

in 1939 and again in 1942. He was invalided home from Gibraltar in 1943 after complaining of dizzy spells. When examined in 1945 he had choreiform movements of the hands and face, gait, speech, muscle tone and tendon reflexes were all abnormal. Electroencephalograph was normal but all air-encephalograms showed large lateral ventricles and diffuse cerebral atrophy. The diagnosis was of pseudo-dementia. In Edinburgh in 1948 he was involved in a charge of indecent exposure and agreed to submit himself to medical treatment. A diagnosis of Huntington's Chorea was now recognised and he was later transferred to Inverness. He was not an easy patient to handle and does not appear to have been employable. Benzhexol Hydrochloride was administered for six months but without effect. Early in 1953 the chorea became worse and he was transferred to the infirm ward where he remained bedridden until his death from bronchopneumonia at the age of 44.

Comment:- A severe case of Huntington's Chorea ending in death at an early age.

P.IV.9. Born 1912.

Heredity:- Daughter of P.III.6.

History:- Patient had a happy childhood and was a normal housewife. Her first two confinements were straightforward in 1933 and 1936. The second two in 1943 and 1946 were both complicated by severe phlebitis. After the last confinement at the age of 32 she noticed the development of a shake in her hands which resulted in some broken dishes.

It was a further eight years before she was admitted to hospital for assessment, by which time the shake had spread to involve the whole body. Examination revealed an iron deficiency anaemia, moderate spasticity, extensor plantar responses and some loss of position sense. Though she was thought to be an unintelligent person it was considered that she had in addition some impairment of memory and apathy. Ferrous sulphate 6 gr. t.i.d. improved her anaemia. Tolazoline 25 mgm. q.i.d. was also administered but without obvious benefit.

When she was admitted to Craig Dunain Hospital four years later it was not because there had been any great change in her own state but rather that the circumstances at home required it for her adequate care. For the present this patient is still in hospital. She is up each day, dressing and feeding herself despite a well marked but not very troublesome athetosis. Speech is very thick and though she can recall her days as a fisher girl she has little memory of recent events. She shows no distress at her present lack of capabilities and is not emotional when talking of her family. The main difficulty she presents is a bad temper with frequent outbursts. For this she is receiving an impressive list of drugs:- Promazine Hydrochloride 50 mgm. t.i.d.; Phenobarbitone 60 mgm. t.i.d.; Benztropine Methanesulphonate 2 mgm. b.d.; Propantheline Bromide 15 mgm. t.i.d.; Amylobarbitone Sodium 360 mgm. nocte.

Physically both speech and gait are affected. All her movements are limited by the sudden jerkiness of her chorea but power is not greatly diminished. There is

no increase of tone nor signs of an upper motor neurone lesion.

Comment:- This patient is showing most of the features shown by her brothers though she has now survived a little longer. Dementia is more troublesome than chorea.

P.II.3. Born 1865.

Heredity:- One of two siblings who were severely affected with Huntington's Chorea. No accurate information can be discovered about the health of either patient.

History:- This man spent a year in mental hospital when he was aged 39. He was stated to have suffered from chorea since puberty but he has been more especially violent for 12 years. At the time of admission (28.12.04) he had advanced mental degeneration. He was violent and had to be restrained from breaking the furniture. His appearance and behaviour indicated imbecility. The examination note states that he had a shaggy beard and moustache. He showed mental enfeeblement. There was perpetual choreic movement of the head and upper limbs. Reflexes were increased. He appeared to have a collapsed vertebra and a swelling beside it (? TB spine). A progress note suggests that the condition was well advanced. He could not walk but spent the day in a chair. A course of arsenic was tried without success. He remained "perfectly quiet and orderly and gives no trouble. It is distressing to observe him." The patient was discharged "Recovered" in 1905.

Comment:- The diagnosis of Huntington's Chorea is twice mentioned in this man's hospital case record (1904). Imbecility appears to form part of the picture in this case.

P.II.4. Born 1856.

Heredity:- Sister of P.II.3.

History:- Admitted to Inverness and District Asylum on 26th May, 1894, not epileptic or suicidal, but dangerous. Certificate from Dr. MacKenzie, Fortrose, states "Hereditary Chronic Chorea." "Easily excited, cries and weeps without cause. She is unable to control activities which are silly and unreasonable." Her father stated that the bodily disease had developed gradually over the past four years. Recently she had had fits of violent temper and was only prevented by force from doing serious injury to others. Dr. Finlayson, Munlochy, thought "the look is of an imbecile." A month after admission she had quietened down and was now talking sensibly, her mental condition improved and the chorea became less obvious.

She remained contented despite grandiose ideas and delusions especially about money. For many years she was "keeping quiet and behaving herself."

In 1899 the chorea was noted to be getting worse and she was mentally enfeebled. The cause of death given by the certificate dated 20.5.1900 was:-

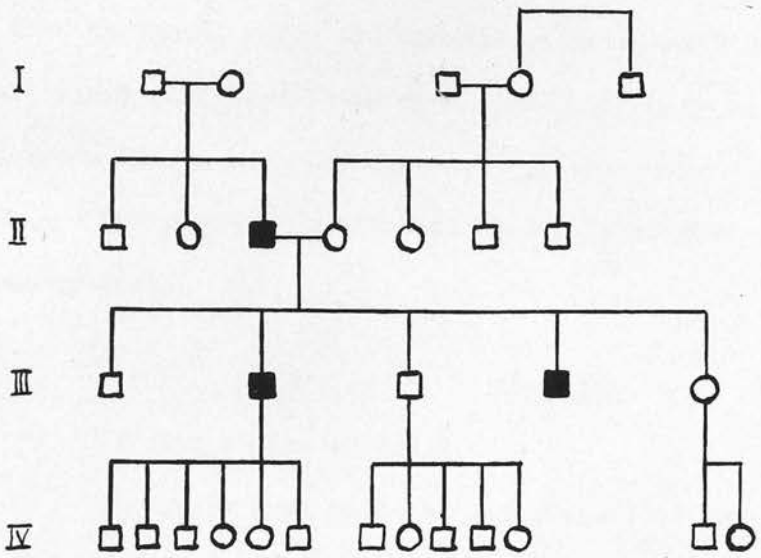
Pthisis Pulmonale - 6 years.

Gangrene of lung.

Chorea - 10 years.

Comment:- Mental deficiency is known to affect this family and may have led to Dr. Finlayson's remarks. Chorea and dementia were certainly present.

FAMILY R



R.I.2. Born 1825.

This lady died at the age of 25 without showing any mental or neurological disorders. One son had Huntington's Chorea, a daughter died at the age of 12 and as the only other son emigrated to Australia his details are lost to this review. For a second wife, the widower took a girl from Buckie and their issue are all unaffected. The implication therefore is that this patient would have developed Huntington's Chorea had she survived.

R.II.3. Born 1852.

Heredity:- Son of the above and father of two affected males.

History:- Born and bred a fisherman this patient is remembered as a courageous and strong man who skippered

a boat for many years and was a leading character in the community. Just after the First War he retired from the sea when he was 68 years old and deteriorated very quickly to his death two years later from a shock. Only in these last years did he have any chorea.

Comment:- A further example of late onset and short duration.

R. III.2. Born 1883.

Heredity:- Son of R.I.2.

History:- From quite an early age this man was regarded has being a 'little peculiar.' This type of description was used by several of his contemporaries but they would say no more than that his behaviour was often strange. His doctor has noted some inco-ordination and lack of expression in his face for the past 25 years but a frank chorea only became obvious 10 years ago when he was 67.

Numerous drugs have been exhibited including Amylobarbitone, Phenobarbiton, Diethazine Hydrochloride, Chlorpromazine and Benztropine Methanesulphate but without greatly influencing his condition.

At present the patient is very frail with a chronic asthma and bronchitis in addition to the chorea. He exhibits a peculiar choking catch in his breath which has been described previously in conjunction with Huntington's Chorea.

Comment:- From the duration of this man's mental condition it is unlikely that this is consequent of Huntington's Chorea which can only be said to have been present for ten years.

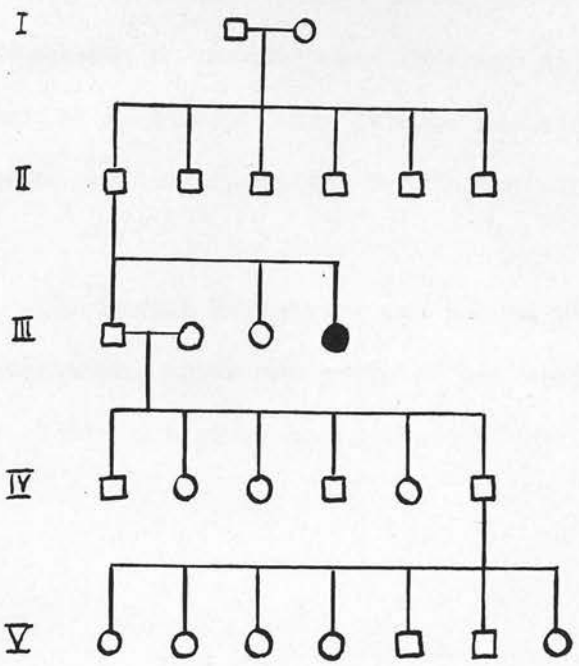
R.III.4. Born 1888.

Heredity:- Brother of R.III.2.

History:- This man was engaged as a fisherman most of his days. When his wife died in 1934 he lodged at Ardersier with his sister. In 1950 he had two attacks of pneumonia for which he was in the Royal Northern Infirmary but at that time no neurological abnormalities were noted. On returning home, he was not only frail but irritable and difficult. This may well have been the early beginnings of the Huntington's Chorea which later developed. In 1952 he was admitted to a hospital for chronic sick but after absconding to Inverness Railway Station in his pyjamas he was transferred to Craig Dunain Hospital. At this time the record states that he was doubly incontinent, very degraded and quarrelsome. He exhibited athetoid movements, continual grimacing and had slurring indistinct speech. No response was noted to Acetylpromazine 25 mgm. t.i.d.; Chlorpromazine 50 mgm. t.i.d. or to Propantheline Bromide 15 mgm. t.i.d. He died of bronchopneumonia on 14th February, 1959.

Comment:- A case of Huntington's Chorea with some degree of preceding psychiatric upset.

FAMILY S



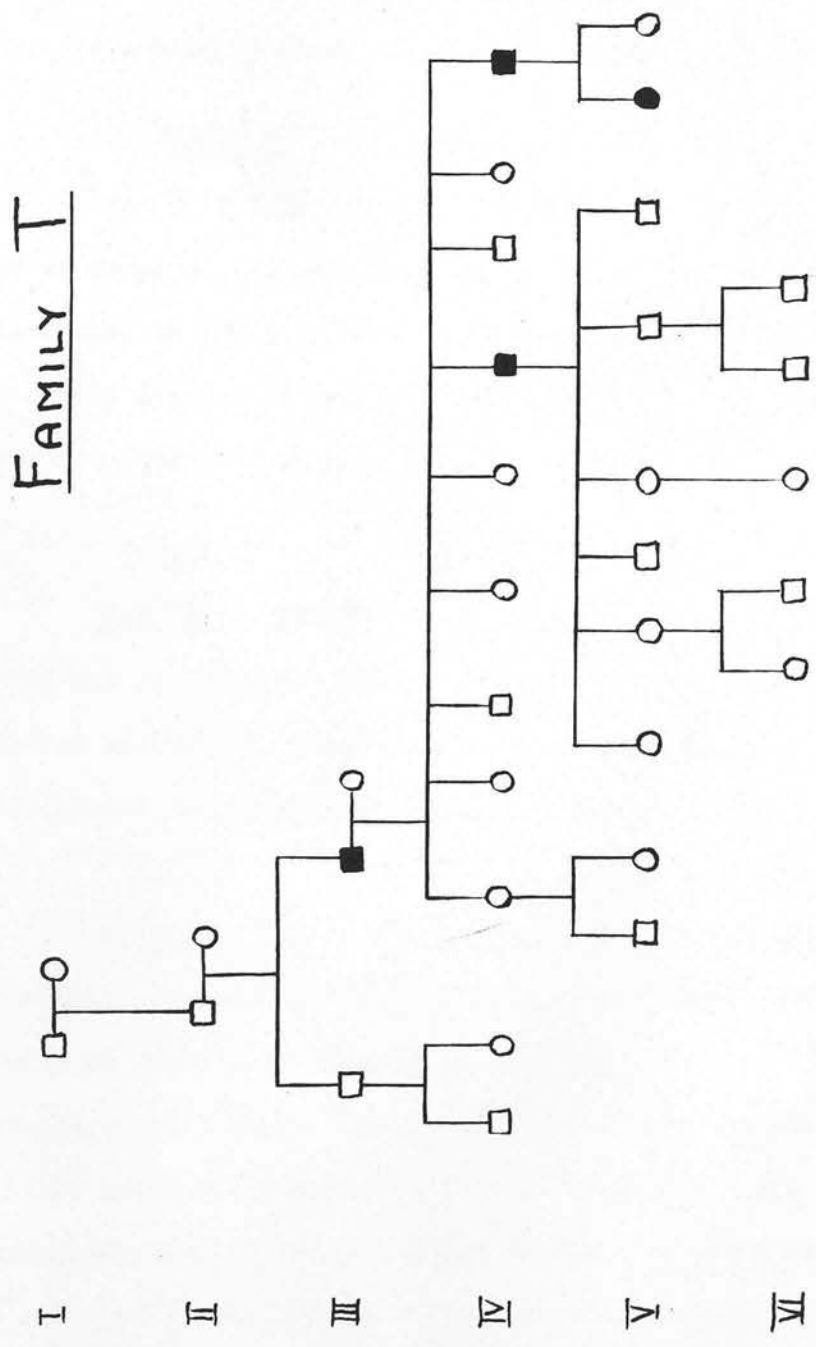
FAMILY S.

The details of this family as described by an old lady are interesting in that they provide a possible link between two families.

The lady's great-great-grandfather (S.I.1.) was born (?1790) of Highland stock with the name of Sutherland. He is known to have come from Brora, is supposed to have married an Avoch girl and to have been drowned in a fishing accident at Dunbeath. One of his six sons was sent to be brought up by aunts at Avoch where he later married. The informant's grandfather (S.III.1.) was a son of this marriage and this line has never been tainted by Huntington's Chorea. Two sisters of this grandfather both married fisherman. One (S.III.4.) went to Peterhead where she raised a family. Later she developed

Huntington's Chorea which was handed on down through later generations. The other sister (S.III.3) was called Mary Sutherland, an unusual name in Avoch and can probably be identified as T.I.2. Her fate is uncertain but it is likely that she introduced the Huntington's Chorea into Family T.

The Parish Registrar, now housed at New Register House, Edinburgh, shows the entry of her wedding on 1st November, 1821, but gives no further information of value.


FAMILY I
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II
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VI

T.II.1. Born 1833.

Little is known about this man who formed the link which this family has with Avoch. He was born in Avoch but his descendants forsook the sea and none has returned to live there. His grand-daughter can just recall him as a very old man with a pronounced shake, working as a milk roundsman with a cart in Forres.

T.III.2. Born 1856.

Son of T.II.1. He was employed as a gardener first at Seapark, Kinloss, Near Forres, but moved to Kildary, Easter Ross, in 1892. Though his memory was good up to the time of his death at the age of 78 he did have a well marked chorea for fourteen years.

T.IV.8. Born 1889.

Heredity:- Grandfather and father had chorea as old men but seem to have had no psychosis and had well-preserved memories. One brother was affected but no children have yet started it though the eldest is 49 years old.

History:- This patient was trained and worked most of his days as a gardener at Brennachie, Easter Ross. Latterly he had a small-holding at Arabella where he eventually died. About the age of 60 he started to become irritable and later this turned into a moodiness. The continual jerking movements started in the arms about that time and this spread rapidly so that when he was admitted to hospital a year later he could not walk. Slurring speech, increased reflex responses and ankle clonus were observed

in addition to the chorea which involved the whole body. Diethazine Hydrochloride was employed in a heavy dosage of 250 mgm. with some improvement in his speech and clearing of his mind but the jerking was not helped. After he returned home he managed to potter about, frequently staggering like a drunkard but was never able to work and died a few months later.

Comment:- Apart from an obvious psychosis this is a classical case of Huntington's Chorea which could not be influenced by the therapy of the day.

T.IV.11 Born 1886.

Heredity:- Brother of T.IV.8.

History:- During the First War this man was gassed and liked to blame all his troubles on this. He settled down as a country postman after the war but soon developed alcoholic tendencies. Drunken outbursts jeopardised his career on many occasions and after his wife died he continued to live in a hovel like a savage with occasional help from his relatives. Athetoid movements started in the hands and gradually spread over the body during the last seven years of his life.

Comment:- Death inthis case was certified as being due to myocardial degeneration. It is confessed by the practitioner that this was to cover the thought that alcohol was the root cause of it all.

T.V.9. Born 1911.

Heredity:- The paternal ancestors for two generations back were known with certainty to have had chorea.

History:- Only the early days of this girl can

have been reasonably normal. During her school life she was an active child and she carried this on with her as she was trained at housework on leaving school. Though a vivacious young lady her marriage to a Londoner was not successful. She was divorced and when her husband got custody of the four children he moved with them back to London. When she was 43 years old she first found she became easily tired and had difficulties with concentration and memory. After some months she became clumsy in her movements, dropping things and also began to stumble. About that time jerking movements were observed especially in her neck and limbs.

When a year had passed a depression appeared and she lost interest in her surroundings. Gradually she became entirely unemotional and her family found they "could command neither her interest nor sympathy." She was admitted to hospital for assessment. She was found to be co-operative, talking without emotion about her children. The speech was thick and slurred. She showed interest in the ward activities. The jerky movements involved her limbs and neck as well as her mouth, tongue and eyebrows. Reflexes were slightly increased symmetrically with some slight increase in tone. Procaine Ammide was worked slowly up to a dose of 1 G. daily but she did not tolerate such a large dose. Chlorpromazine 25 mgm. t.i.d. was next exhibited with some improvement in her depression but no real change could be claimed in her general condition.

On returning home she struggled on for a further 18 months becoming less and less able to look after herself

so that she had to be admitted to the care of Craig Dunain Hospital.

The combination of Reserpine 0.25 mgm. t.i.d. and Amylobarbitone Sodium 120 mgm. b.d. reduced the excessive movement sufficiently to allow her to walk more easily. A sufficient improvement in her appearance and feeling of general wellbeing were induced by regular care and good feeding, to allow the suggestion of returning home on an indefinite pass, but the home conditions were not adequate to permit this and the arrangement was cancelled. At present this patient is lying totally confined to bed and completely demented. For her bad temper she receives Chlorpromazine 100 mgm. t.i.d. but even so she has to be fed as she is liable to throw utensils and food. The involuntary movements are not a great trouble to her now being of small excusion. Her movements are, however, greatly restricted by poor motor power and co-ordination. The limbs are held in a state of flaccidity most of the day and there are no signs of involvement of the pyramidal system.

Comment:- This case illustrates the onset of Huntington's Chorea at an early age. Psychosis has been minimal. Chorea is not as marked now as the severe dementia.

ANALYSIS OF CLINICAL DETAILS

It should be emphasised that all the medical histories detailed on the preceding pages have been verified. The family trees do not show affected people whose particulars cannot be corroborated even though they are suspect. Some belong to previous generations, some have emigrated and for many there are no medical notes available.

Whereas the existence of choreiform movements can be accurately determined by careful questioning, the psychiatric aspects often become very confused. Mental deficiency runs through some families. Degenerative changes, whether from alcohol or senility, appears in many members of the older age group and, in the absence of a detailed clinical assessment before they died, the exact diagnosis defies clarification. Occasional examples of other organic psychosis are to be found in this community and some of these have misled the local worthies.

As many of the affected people have been hidden away in their latter years the outside world never knows the details and the families would never reveal honestly the psychiatric state of the patients.

It is therefore practical in a large number of cases to consider only the symptom of chorea.

Source of the disease:- A spontaneous mutation of genes occurring in this spot is not a likely explanation of the presence of Huntington's Chorea in this community. More probable is the idea that the disease was brought in by fishermen who settled here about 300 years ago.

Seven families have been described in detail in

in this series and it is highly probable that they can all be linked together at an earlier stage to show a common source. They have been traced back for about 150 years in most instances but, as so many uncertainties are associated with information earlier than this, it is quite untrustworthy and an origin common to these seven families has not become apparent.

The late Professor Smith Ely Jellife of New York (34) encountered this difficulty when engaged in a similar research on a family with Huntington's Chorea and has remarked that "the amount of time consumed is out of all proportion to the results obtained." With this precept, attention will therefore be focussed on the material available so far.

The family trees show 44 patients who are considered to be afflicted with Huntington's Chorea. Twelve patients are still living and, of the remainder, there is no certain information about age of onset of symptoms in three cases. The significant facts are tabulated for convenience.

PATIENT	DATE OF BIRTH	AGE OF ONSET	AGE AT DEATH	DURATION	REMARKS
C.II.5	1844	65	68	3	
C.II.1	1835	59	65	6	Alcoholic
C.III.2	1868	50	55	5	Exposure
C.III.7	1867	57	69	12	Alcoholic
C.IV.14	1893	40	52	12	
C.IV.13	1896	50	LIVING		
C.IV.6	1911	40	LIVING		
C.IV.9	1910	42	LIVING		
C.III.5	1871	61	63	2	Cerebral Thrombosis
K.II.2	1820	65	80	15	
K.III.8	1862	75	80	5	
K.III.3	1840	69	80	11	
K.IV.26	1892	48	58	10	Colonic Carcinoma
K.IV.32	1896	59	LIVING		Religious
K.IV.1	1879	70	75	5	Cerebral Haemorrhage
K.V.2	1920	31	LIVING		
L.II.2	1860	30	40	10	Alcoholic
L.III.5	1884	33	38	5	? Suicide
L.III.7	1889	29	31	2	
N.III.10	1860	74	75	1	
N.II.15	1849	72	74	2	Cerebral Thrombosis
N.III.27	1884	64	75	11	
N.III.18	1863	71	78	7	

PATIENT	DATE OF BIRTH	AGE AT ONSET	AGE AT DEATH	DURATION	REMARKS
N.V.1.	1899	41	LIVING		
N.V.2	1902	40	LIVING		
N.V.3	1904	42	LIVING		
N.V.4	1907	48	LIVING		
P.II.12	1846	44	49	5	Pthisis
P.III.6	1869	55	58	3	
P.IV.5	1902	42	54	13	Cerebral Thrombosis
P.IV.8	1911	34	44	10	Indecent Exposure
P.IV.9	1912	32	LIVING		
P.II.3	1865	27	41	14	
P.II.4	1856	34	44	10	Pthisis
R.II.3	1852	68	70	2	Cerebral Thrombosis
R.III.4	1888	65	71	6	
R.III.2	1883	67	LIVING		
T.III.2	1856	64	78	14	
T.IV.8	1889	60	62	2	
T.IV.11	1886	56	63	7	Alcoholic
T.V.9	1911	42	LIVING		

Incidence:- Until recent times, the people of Avoch seldom married outside their own village and it would be highly misleading to attempt to estimate the incidence in Scotland or even in the county from this material which has been drawn from such a localised community.

An approximate figure of 5 per 100,000 has already been quoted as the incidence in Cornwall, Northamptom and the United States. This can be more appropriately expressed as an incidence of 0.005%.

The village of Avoch has at present 896 names on the Voter's Roll, that is, in October, 1959, there were 896 people over the age of 21 who were officially domiciled within the confines of the village. Although 12 patients described in these families are at present alive, only 5 were born in Avoch representing an incidence in the village at present of 0.56%. Expressed differently, this means that to be born in Avoch increases by about 100 the chance of developing Huntington's Chorea compared with these other larger areas,

Many people have claimed locally that there are fewer cases in Avoch now than in former times and this may be so because improved transport has coincided with a breaking down of barriers, allowing a wider scatter of cases than was previously found.

Age of onset:- In 41 patients the average age when symptoms started is 51.59 years (S.D. $\pm$ 15.6). The earliest onset of symptoms is at 27 years (P.II.3). The latest is at 75 years (K.III.8). Between these extremes there is a wide scatter as seen in Fugure III where the cases are grouped in the decade in which symptoms were first

noted.

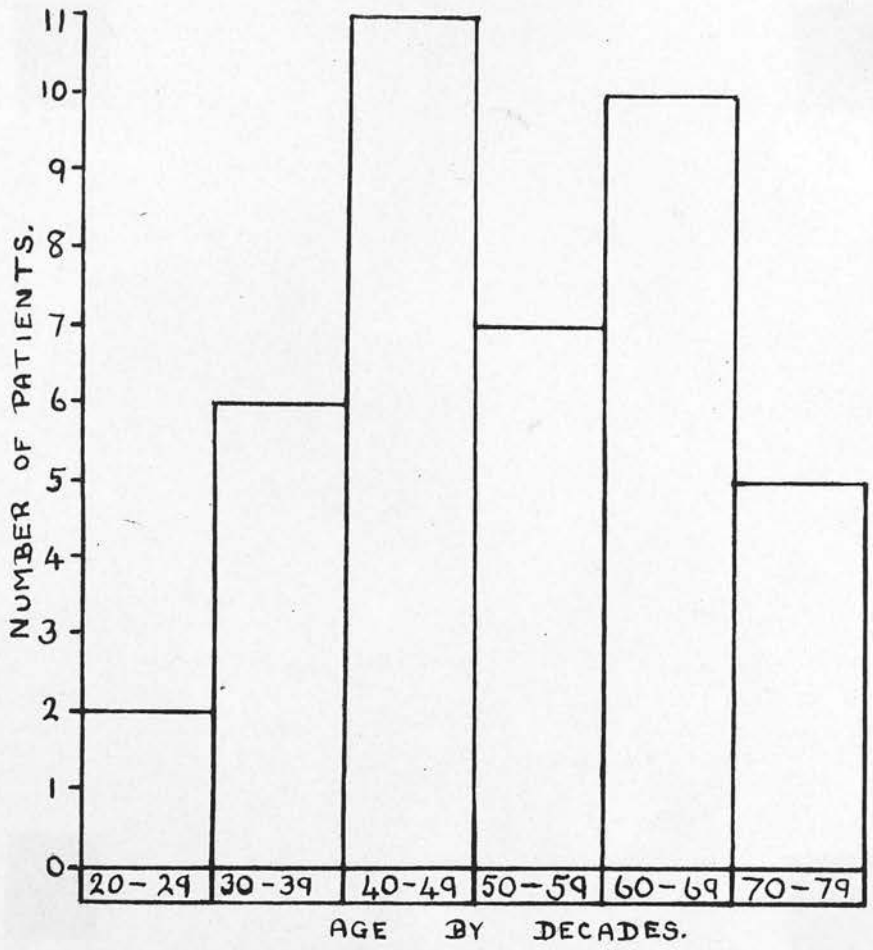


Figure III - Showing the age of onset of chorea in 41 cases.

Comments:- This average age of onset at 51.59 years is rather higher than the figure usually quoted. Kinnier Wilson (21) gives an average of 37.1; Davenport (7) reviewing a large series of published cases finds an average of 35.5 years.

The maximal incidence shown in Figure III falls in the ages 40-49 and it is noteworthy that the symmetry of the graph is upset by an incidence almost as great in the ages 60-69 which may be responsible for the average age of onset being so high in this series. This may be the fault of having such a small number in the series or

conceivably there might be two distinct bio-types appearing in the village. This double peak could also be used as evidence to support the occurrence of "Anticipation" in Huntington's Chorea. This will be discussed later.

Bearing in mind that the disease process has been active for an indefinite time before the chorea is first manifested, a possible explanation of the later onset may lie in the changing local conditions, the apparently high infant mortality rate of former times and the prevalence of tuberculosis in the village which may have killed the weaker individuals before they could develop the disease.

Duration:- The average time that patients have survived after first exhibiting chorea has been calculated as 7.13 years (S.D.$\pm$ 4.5) in the 29 patients who have died. The longest is 15 years (K.II.2). The shortest was only one year (N.III.10) but the exact cause of death has not been discovered in this case. Twelve patients are still surviving, having shown symptoms for 5 - 20 years.

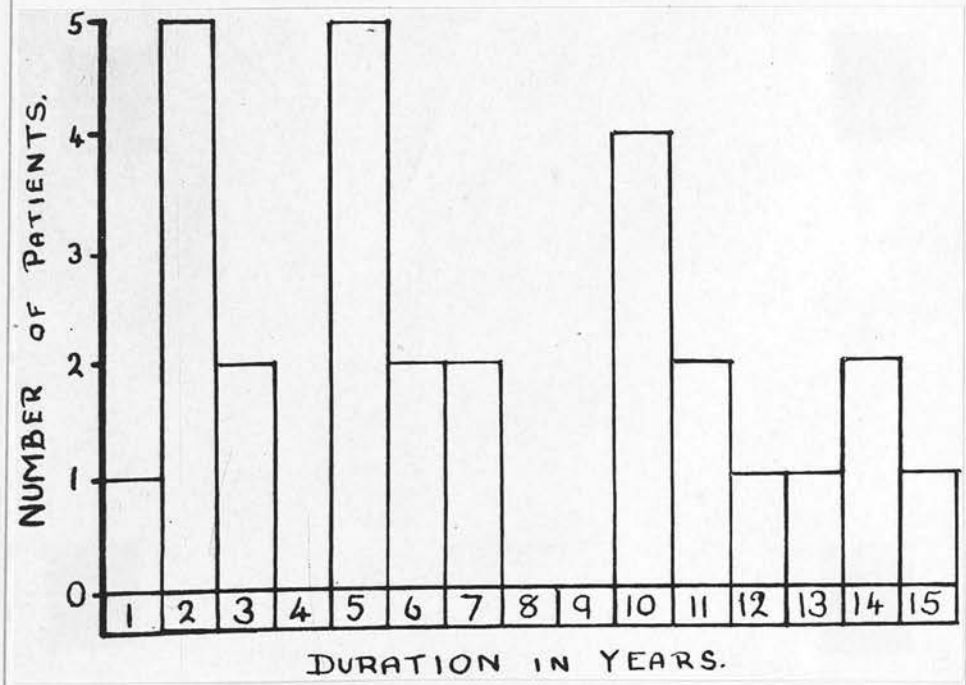


Figure IV:- Showing the survival time in 29 patients after the development of chorea.

Comments:- Incidental disease obviously influences the duration of life in any section of the community, and must affect the results of this series. Unfortunately our numbers are too small to make it worthwhile introducing a correcting factor from, for example, the Registrar-General'S returns. Poverty, tuberculosis and alcoholism must have had a great influence in this village particularly in the past and for the younger people while degenerative conditions are of more concern at the present and to the elderly. Five of the patients in this series died of cerebro-vascular episodes at the ages of 54, 63, 75, 74 and 70 after having had symptoms of Huntington's Chorea for 13, 2, 5,2 and 2 years respectively. The first of these (P.IV.5) seems to have had the additional hazard of hypertension. Thus the fact that many of our cases were older than the usual average distorts the picture by introducing causes of death other than those directly associated with Huntington's Chorea.

The appearance of Figure IV suggests that there are two populations represented on the graph. One group may survive for 6-7 years while the other group falls mainly into the 10-14 year period. It has been felt previously that the survival time of a patient may depend on the age at which symptoms were first noticed and this will now be examined.

Correlation of Duration with Age of Onset:- With the number of patients available in this series it is appropriate to combine the previous two figures in a scatter-graph.

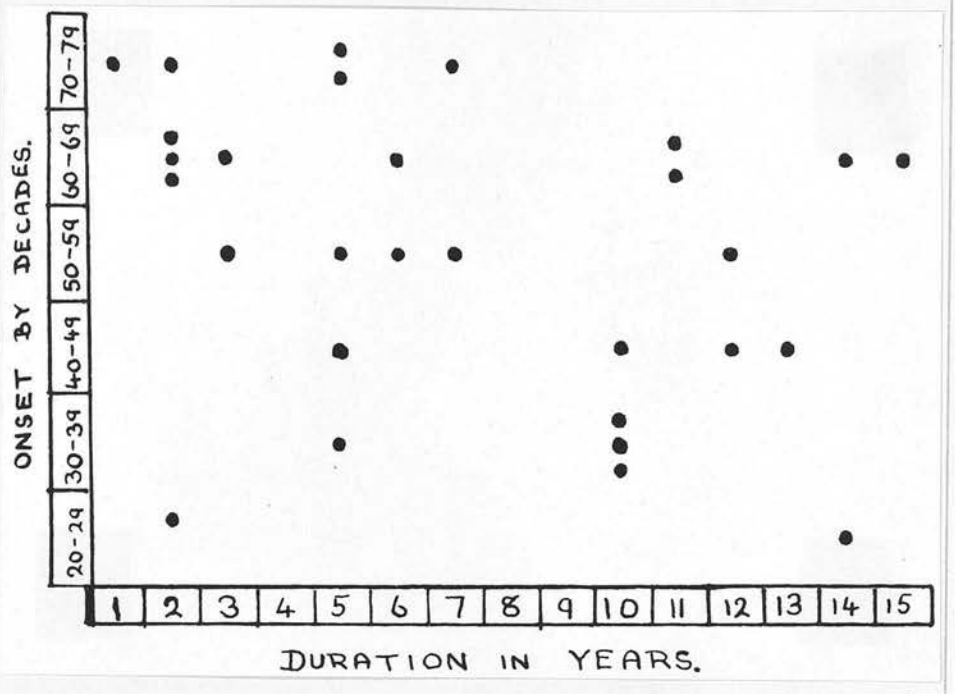


Figure IV - Scatter-graph plotting survival time and age of onset of chorea in 29 patients.

Comments:- A wide scatter is evident in this graph. The slightly increased density in the upper part of the graph may be expected from the previous observation that our patients are somewhat older than the average. The density of the upper left quadrant is in keeping with the comments that old age has its own hazards irrespective of Huntington's Chorea.

With this single exception, however, it does not appear that people who are affected early in life survive only a short time. Neither does the converse hold that elderly people can carry on for years.

Severity of Symptoms:- The local medical records only go back for 25 years and the hospital records prior to this are sometimes scant. It is regrettable that insufficient data is available because of this to form the basis of useful comment about the severity of the disease.

A wide range has been shown amongst the cases already described. At the one extreme cases T.III.2 and C.II.5 suffered no more than incessant nodding of the head and do not appear to have sought medical help. These can be contrasted with the very fully developed cases P.IV.5 and T.V.9. who were so incapacitated by chorea that they were unable to dress or feed themselves.

Heredity:- In a disease such as Huntington's Chorea which is carried from birth but only manifests itself in adult life, family trees must be analysed with great reserve in a community with a high mortality rate both for children and fishermen.

For the calculations of this section, children under the age of 30 have been omitted. On the other hand, people are included who are strongly suspected of carrying the gene even though this cannot be proved.

Huntington's Chorea is regarded as a hereditary disease due to dominant gene and therefore with a theoretical average chance of inheritance of 50%. In different series this has varied from 30% - 55%. Our pedigrees show that 20 affected parents had 108 children of whom 27 were affected, a 25.93% chance of inheritance. While these figures can be further broken down as in Table III it must be remembered that each section has very small numbers of cases and any conclusions may be open to debate.

AFFECTED PARENTS	CHILDREN				
	Affected		Clear		
	Male	Female	Male	Female	Total
Mother 6	3	4	15	10	32
Father 14	12	8	29	27	76
Either 20	15	12	44	37	108

TABLE III - Showing the numbers and condition of children from parents affected with Huntington's Chorea.

A further examination is suggested by the large number of affected children from affected fathers to find if there is any significant sex inheritance. This is set out in Table IV.

HUNTINGTON'S CHOREA.

Parent	Present	Absent	Total
Mother 6	7 (8.1)	25 (24.3)	32
Father 14	20 (18.9)	56 (56.7)	76
Either 20	27	81	108

Expected figures are bracketed. $X^2 = 0.188$ at D.F.3.

Table IV - Showing an analysis of sex inheritance of Huntington's Chorea.

Comment:- These figures show that the sex of a parent is unimportant in the inheritance of Huntington's Chorea in this series. In the families under review at present there is a lesser incidence of the disease amongst the children of affected people than is commonly reported. Even though more males have been affected it has been shown statistically that males do not have a greater chance of handing on the disease than do the females in this series.

As the explanation of this male preponderance it might be claimed that the general population normally contains a slight excess of males. This can be illustrated by enumerating all children shown on the above family trees whether or not they are in affected families. One hundred and sixty males and one hundred and fortytwo females are shown, hardly enough to account for our preponderance and a wider search must be made particularly into the social customs. Traditionally these fisher-folk seldom married beyond their own community but while investigating the ancestry, it was remarkable how often a man from Avoch brought a bride from some other Moray Firth port but how seldom it was the groom who moved to Avoch. Many of the mothers in this series are therefore off untainted stock. Another possible explanation is in the somewhat unromantic courting customs which were strictly observed even during the times which are still remembered. Thus a girl from an affected family would have a poorer chance of matrimony and she must never take the initiative.

Bilateral Inheritance;- Consideration so far has been given to families where only one parent has been affected with Huntington's Chorea. This series is exceptional in containing a family in which the mother and probably also the father were carriers of the disease. The tragic family N.V.1-4 are all at present in Aberdeenshire Mental Hospitals suffering from Huntington's Chorea. Their mother died of tuberculosis at an early age but her mother was a known sufferer though it has never been clear to which family she is related. The father is not supposed to have exhibited any chorea but as his father

came from Family S and his mother was a sister of a known case he himself has two chances of acquiring the abnormal gene. That Huntington's Chorea has been proved in all four siblings of this family is strongly in favour of the idea, held locally, that both parents transmitted the disease.

The factors which influence the number of siblings to be affected are still obscure and as yet unproved. It may be that the penetrance of the gene can vary or it may be that more than one gene is concerned with the production of the chorea. Thus if an alellomorph is transmitted, causing the disease, the severity, age of onset or incidence in a family may be influenced by these other modifying genes.

Anticipation is a feature of hereditary disease where the symptoms start at an earlier age in each succeeding generation. Both Davenport (7) and Bell (35) analyse large series of cases and by calculation discount the importance of this in Huntington's Chorea. Some of our families do give the impression that anticipation is occurring but there are insufficient generations detailed to show a true pattern and an insufficient number of cases to withstand statistical analysis to settle this problem. An overall picture of four of the likliest families is set out in Table V.

Generation	Family			
	C	K	P	T
I				
II	65 59	65	44	
III	50 57 61	75 69	55	64
IV	40 50 40 42	48 59 70	42 43 32	60 56
V		31		42

Table V - Showing the age of onset of chorea in some patients arranged according to their generation in their families.

Comment:- These crude figures destroy the impression gained during the case-taking that anticipation would be obvious in this series.

Fertility:- Even a casual survey of the pedigrees shows no evidence of infertility amongst patients with Huntington's Chorea. Figures have not been produced to support this statement because it would be excessively difficult to make them accurate. Celibacy has been proved in only one family as already mentioned (L.II.2) but may well have been practised silently by other individuals. Sterilisation was carried out on one patient (K.V.2).

The strict morality of these fishermen and their families who have been under scrutiny is noteworthy. Illegitimacy rates are not available for the village but in the county the figure of 4.4/1,000 live births compares well with the average for the whole country at 4.2/1,000. It has been claimed before that a low rate of illegitimacy usually signifies a high degree of knowledge of contraception rather than reflecting morality but this is too cynical a view to hold of poor but hardworking fisherfolks.

In pursuing the ramifications of the family trees only one wanton character has been encountered (viz. P.II.5) who hadtwo illegitimate children. Liaison might have been expected from the menfolk when visiting other ports of the north-east of Scotland but all the cases of Huntington's Chorea which have been discovered are the issue of legal unions. This is in strong contrast with the American writings but agreed with the reference already made by Russell Brain.

Non-hereditary chorea:- The appearance of Huntington's Chorea in patients whose parents have been free from the disease is always the subject of debate. This might be suspected in 6 families in our pedigrees but in these instances the parents either died young or before the correct diagnosis had been recognised. This investigation has shown how very intertwined the relation-:ships of the families are in this village and as so many cases of Huntington's Chorea are found there is hardly any need to postulate that the disease has started spontaneously in any of these cases.

Families A and B. hold aspecial place in this respect and some aspects have already been discussed. From the account of the delusions of case B.III.3 one is tempted to employ the classification of Paracelsus and suggest a diagnosis of Chorea Lasciva.

Illegitimacy has already been suggested for these isolated cases. This is not a likliehood, however, as neither is the first born in the family. In a countryside where a test of fertility often preceeds matrimony it is usually the eldest child who is illegitimate. Bell quotes

several authenticated cases from the literature of chorea is sibships where their parents were unaffected even though they were quite old at death. She concludes "It would be contrary to all experience of hereditary affectations if cases did not occur occasionally, indistinguishable from those diagnosed as Huntington's Chorea ... but providing no evidence of genetic determination of the disease." With this we would agree. It is worth suggesting that chorea is a syndrome which might arise as a result of different pathological processes such as infection, tumour or thrombosis so long as the resultant damage was in the correct anatomical site. The term Huntington's Chorea should be reserved therefore for the hereditary chorea which implies a single and definite cause.

Blood Group:- The arguments laid out already are clear proof that Huntington's Chorea is not transmitted on a sex chromasome. That the alellomorph is unconnected with the blood groups has already been shown by the very detailed work of Pleydell (9). Observations with these cases are similar to this work and while there are only seven living cases in this locality examples amongst them fall into groups AB, B and O with rhesus positive and rhesus negative.

Electroencephalogram:- While searching for an accurate means of diagnosing Huntington's Chorea early, Paterson (23) suggested the use of the electroencephalogram and claimed that the pattern of the tracing was specific for this condition. He described (1) dominant slowing of waves (2) sudden high voltage, episodic slow or fast bursts (3) abortive or genuine bilateral spike and wave

formation (4) exaggeration of above by hyperventilation. Harvald (24) refuted this by showing that these changes were sometimes absent in clearly well established cases. It has been practical to arrange electroencephalograms in only five of our cases and for the non-hereditary case A.II.5. In each of these only non-specific changes were reported.

Developmental defects:- Careful search and enquiries from many different angles failed to discover any congenital deformity or disease common to this community beyond the mental deficiency already mentioned. Backwardness and deficiency occurs sporadically in the village to a greater extent than would be expected but it also runs in families which are unassociated with Huntington's Chorea. Intermarriage in the extreme degree practised in Avoch must to some extent be responsible for the mental deficiency. Both this feature and the many other social complications of the village make it quite impossible to clarify further any possible association between deficiency and Huntington's Chorea in Avoch other than to state that both are found but do not appear to be connected.

PSYCHIATRIC ASPECTS

Many people who have had practical dealings with the early stage of Huntington's Chorea prefer to base their diagnosis on behaviour changes rather than on neurological features. Yet the real psychosis occurs in most cases a few years after the chorea is established. This appears to be paradoxical and yet it agrees with my own experience of the early or pre-Huntingtonian state. Moodiness,

depression, irritability and neglect of home and person are all features which have been exhibited by one or other of our patients. With two cases there is a marked periodicity about these symptoms though no true precipitating factor has as yet been observed. Both with K.V.2 and C.IV.13 the house is the best index of the patient's condition. For months it will be clean and tidy but then for no obvious reason there will be a month or so of neglect and disorder.

Some of the external influences which affect Huntington's Chorea can be inferred by the behaviour of these patients when they are admitted to general medical wards whether it be for investigation, treatment or for an incidental illness.

Excitement tends to make the chorea more marked and these patients tend to be more excitable than normal. They may be made worse by the excitement of attending an Out-Patient Clinic or being admitted to a ward and many have claimed that they are made worse even by a visit of friends to their homes. From our records it appears that many patients have deteriorated when they arrived in a ward and gradually improve over 2-3 days without any specific treatment as they settled to their new surroundings.

Neglected nutrition and personal tidiness are often found in affected patients and a great improvement in mental and physical wellbeing has usually been apparent after these are corrected in hospital or when the patient is induced to live with relatives.

Incidental febrile illness such as influenza has often been found to accentuate the choreic symptoms in our patients.

The influence of alcohol and the improvement following abstinence has been seen often in this series. Alcoholism seems to have been prevalent at the end of the 19th century but it is uncertain why this should have been so. Perhaps if spirits were cheap they formed an easy escape from the poverty, endless worries, ill-health and poor living conditions which prevailed at that time.

Drunkeness has been mentioned in some clinical histories above but does not seem to have been specially associated with the cases of Huntington's Chorea. Our most noticeable cases were P.II.3, C.II.1 and C.III.7. From the case record it would appear that the last of these improved considerably in physique when he was weaned off it in hospital.

Religious tendencies were noted in some patients but only assumed serious proportions in the cases of K.IV.32 and N.III.27. Superstition and religion are intertwined with the life of any fishing community and are well in evidence in Avoch.

Features of persecution were present in C.II.1. Marked aggression was noted with P.II.12 and the behaviour of P.III.6 and P.II.4 was described as grandiose. It is possibly a reflection of modern forms of therapy that psychoses are not so evident in the cases still living. Dementia has overshadowed any chance of one in T.V.9 and P.IV.9. Manic-depressive reaction has been observed in three of the patients who will be studied later in more detail.

Changes in the methods of handling mentally disturbed patients can also be followed with interest over

the years. Some of the hospital records of last century give great prominence to the fact that some of the patients "threatened to do harm to themselves" and "has threatened suicide" but this has hardly been seen in the last fifty years.

Suicide:- "That form of insanity which leads to suicide" is part of Dr. George Huntington's original description of the disease. So far as can be ascertained, however, this happened only once in the present series when a young man who realised the implication of his condition after emigrating to America waded out to sea and was drowned off Long Island. Bickford (8) observed a high incidence of suicide and gives this as a reason for some of his cases being awarded for gallantry during the past war. In the North-East of Scotland, however, the "Avochie" has always had a reputation for skill, endurance and courage (apparently described over two centuries ago by Admiral Parker when he press-ganged some men on to the boat, Indomitable). This is probably a feature of the breed whether affected or not and one can readily recognise the complete lack of insight both in the younger men of today showing early signs and in the tales still circulating about their ancestors, which makes it unlikely that self-destruction need be feared at Avoch.

Sexual forms of mental disturbances have already been observed by American writers who claimed that it was commonly part of Huntington's Chorea. This tendency has been denied by Brain and does not occupy a prominent place in the accounts in this country. P.IV.8 was the only case in our community to have been guilty of this.

He was convicted of indecent exposure to girls in the same lodging house in Edinburgh and after he reached Craig Dunain Hospital caused similar embarrassment to the Occupational Therapist.

Neurology:- Accurate information about the neurological changes is present for a very few of the cases in this series but a useful guide can be obtained from examination of the patients still living. Apart from variation in degree of involvement of the body by athetosis which has already been shown to cover a very wide range, it is noteworthy how uniformly absent the neurological findings are. An increase in muscle tone has been found in an occasional case (e.g. K.IV.26), indicating an extension of the disease processes to neighbouring areas to produce a Parkinson-like element to the symptoms.

The chorea itself has almost always followed the classical description, starting with a restlessness or jerking about the head or upper limbs. This tends to spread over the body as it becomes more severe but the speed of this advance varies considerably amongst patients. The fully established case is continually on the move during waking hours to quieten completely only while asleep. The head is frequently jerked to the side or up and down. Grimacing and disordered movement of the tongue causes a dyslalia. Movements of the arms are purposeless and may be quite extensive in some while others have no more than a continual fumbling of the hands. Many patients develop tricks of anchoring the hands by tucking them into their clothes or sitting on them to lessen the disturbance of the chorea. Frequently the trunk gives sudden jerks which often throws the patient off balance and some learn to stand

with their feet well apart for stability. The walking of patients with advanced chorea often has a staggering quality but less affected patients will be found to walk surprisingly well though when sitting on a chair the feet are continually on the move. Headache may be associated with Huntington's Chorea and has been a particular trouble of C.IV.13 in whom it can be reasonably controlled by salicylates. Some loss of motor power has been observed.

No sensory changes are to be found in these patients, neither has there been any associated disturbance of the special senses.

None of the cases examined has shown any jerking of the eyes. There have been no cases with any upset of swallowing.

Involvement of the respiratory muscles by chorea has been mentioned by Julia Bell (35) as a great rarity, only one case being present in her large series. An example of this complication is to be found in case R.III.2. From time to time this man has phases of a peculiarly jerking and wheezing respiration which sometimes may become severe and alarming. On one occasion his practitioner was called out in the middle of the night and found the patient near death, lying stiff and pallid across the bed. An injection of cardophyllin and adrenaline revived him and he was able half an hour later to enjoy a drink of tea.

The early neurological changes in a patient developing Huntington's Chorea are a source of difficulty. Anxious relatives must often fear that fidgeting with the hands or even the shrug of a shoulder is a significant

sign in a person with choreic forebears. Psychiatric changes are in my experience likely to give a better guide to early Huntington's Chorea and neurological changes are better reserved for confirmation.

TREATMENT

In ancient times some patients with chorea are said to have had their heads opened to allow the escape of the devils with whom they were afflicted. Vessie (39) has described how the people of Connecticut used to regard these patients as witches and burned many of them.

As has been already quoted from George Huntington's original description (6) he recognised that "treatment seems to be of no avail." As late as 1952 Brain (1) states that no form of treatment is known to arrest the progress of the dementia or to control the involuntary movements. In 1954 Kinnier Wilson (21) can only offer institutional care for the choreic. Treatment by drugs has often been sought. Various different substances have been claimed as cures but have not shown up well in practice.

A suggestion by Tomlinson (25) that an extract of Bulgarian Belladonna was helpful was denied by De Myer and Dyken (26)

The use of Bulgarian root as a source of Belladonna was popularised in 1938. Its special qualities were later discounted when it was shown that its superior strength was due solely to the method used to extract the alkaloid. Later it was discovered that on an occasion when the Bulgarian harvest failed, the dishonest merchants

supplied an ordinary root and no difference in potency was noted by the users.

Goldman (27) conducted a trial with Procaine Amide after the chance observation that a patient with Huntington's Chorea relaxed well in a dentist's chair following an injection for an extraction. He recognized that the response varied in different people but found all his patients benefited to some extent. When the drug was stopped the symptoms took a week to return. De Myer and Dyken (26) disproved this claim also. They did report a subjective response but showed no improvement in any of their patients. Sudden withdrawal caused no exacerbations. Lazarte (28) in his study of 19 patients also denied any improvement with Procaine Amide. This lack of significant response has been borne out in our cases described above.

Reserpine:- Was advocated by Chandler (29) and Lazarte (28) but subsequent work has not sustained their claims.

B.A.L. was used by Nielsen (30) who reported poor results in Los Angeles.

Prophylaxis:- Many writers have advocated that persons of affected stock should abstain from having children. The symposium from the Mayo clinic (10) shows a determined effort to check the rising incidence in America by eugenics. Pleydell (9) in this country recommends that Roman Catholics should be advised against marriage and Protestants advised against procreation. He feels that Medical Officers of Health should be prepared to follow up cases and advise practitioners of the hereditary nature of the disease.

Eugenics has obviously been considered in Avoch, at least by the local practitioners, but without meeting any great success amongst the affected families. These fishing families do have peculiarities of their own and advice on such a subject or any encroachment on their personal liberties is not well received.

While occasional individuals have remained single there is an example of one mother (L.II.3) who had so much trouble with her husband that she persuaded and prevented her children from marrying. Only her youngest boy disobeyed her. He begot three children who are now approaching 50 years of age without manifesting any trace of Huntington's Chorea.

In more recent times, one patient (K.V.2) has been sterilised on medical advice.

Sedatives must have formed the basis of most schemes of treatment for Huntington's Chorea up to about ten years ago and of the preparations then available Phenobarbitone seems to have been the most widely used. In more recent times many new drugs have become available and some of these have been used on our patients.

Details are available about the drug treatment of fourteen patients in this series and some interesting features can be noted. Firstly, however, it is worth considering a few of the difficulties which have prevented this data from being surveyed in a table or graph:-

1. Dosage of the drugs varied.
2. The observations are made by numerous doctors with varying interests.

3. The patients have all been at different stages of the disease when under treatment.

4. Some of the patients were not affected; others were dead when some of these drugs were being used.

5. A note claiming improvement in a patient does not always refer to which aspect is being considered. Some are in fact precise and state for example "patient's walking is improved" or "Chorea is less" or again "patient is less depressed."

6. Polypharmacy especially adding a small dose of Phenobarbitone to other drugs has been commonly practised.

Phenobarbitone was administered to all but one of the patients and as might be expected it was particularly the early cases which benefited most. This drug should therefore be tried in the early stages of the disease and where the patient's condition is still liable to be made worse by excitement. Later on when the patient is in a pathological state of excitement a sedative may be indicated again.

Amylobarbitone has also been used but on fewer of the patients. It has shown a higher success rate than with Phenobarbitone. Some of this reflects on differences in the hospitals, therefore in the condition of the patients in that the general medical wards were more inclined to use Amylobarbitone than the hospital for nervous disorders.

For the most part patients who did well on

Amylobarbitone had also been helped by Phenobarbitone but there were two patients who did rather better. After a study of the case records this can be ascribed to a slight improvement in the physical condition of the patient while they were in hospital.

Bellergal was given to one patient only (K.V.2) but without any noticeable benefit. This compound consists of total alkaloids of Balladonna, Ergotamine tartrate and Phenobarbitone.

Tolazoline was ordered for three patients (C.IV.13, P.IV.5., P.IV.9.) who were at that time all in the early stage of the disease but no help accrued.

Only two patients (P.IV.5 and T.V.9) who were both young were tried with Procaine Amide. Neither was helped but this may have been because the drug was administered orally instead of starting with a parentral course which has been recommended.

Reserpine failed to help two patients (C.IV.13 and T.V.9) who were both young.

Mephenesin did not improve either of the patients (P.IV.5 and K.IV.32) to whom it was given orally. This appears to have been used empirically though one of the patients (K.IV.32) did have some increase in muscle tone.

Another drug which was apparently tried empirically was Propantheline but neither patient P.IV.9 nor R.III.4 were improved at all.

Phenothiazine Compounds:- The other chemotherapeutic substances used in these cases of Huntington's Chorea are all derivatives of Phenothiazine and this group

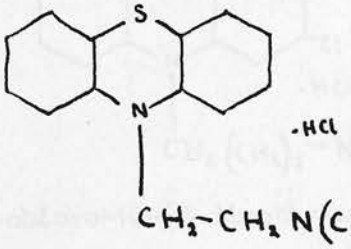
of drugs might well be considered in detail. Roughly, they can be sub-divided into (a) the antihistamines which have not been employed for Huntington's Chorea in this locality.

(b) those used for Parkinsonism, represented here by:-

1. Diethazine
2. Benzhexol
3. Ethopropazine
4. Benztropine.

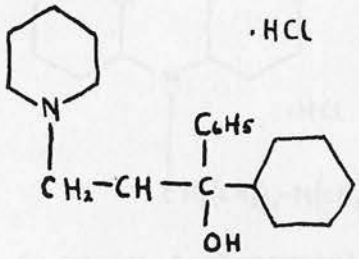
and (c) those in which the sedative action is mainly used:-

1. Chlorpromazine
2. Promazine
3. Prochlorperazine
4. Acetylpromazine.



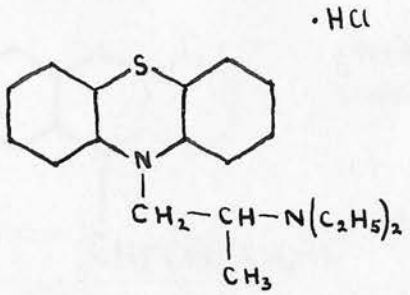
DIETHAZINE HYDROCHLORIDE

10(2-diethylaminopropyl) phenothiazine Hydrochloride



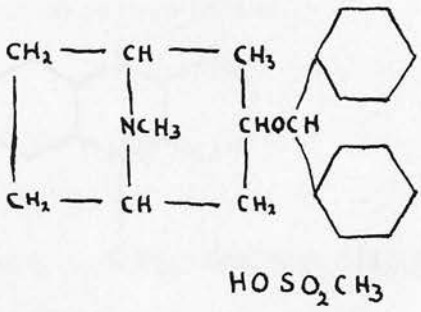
BENZHEXOL HYDROCHLORIDE

1-cyclohexyl-1-phenyl-3-piperidinopropan-1-ol Hydrochloride.



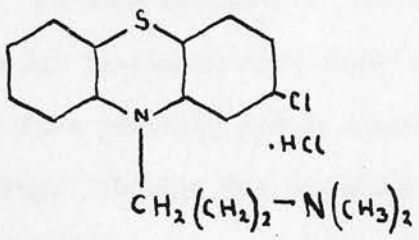
ETHOPROPAZINE HYDROCHLORIDE

10-(2-diethylaminopropyl) phenothiazine Hydrochloride



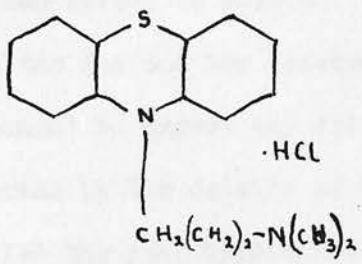
BENZTROPINE METHANESULPHONATE

3-(diphenyl methoxy) trophane Methanesulphonate.



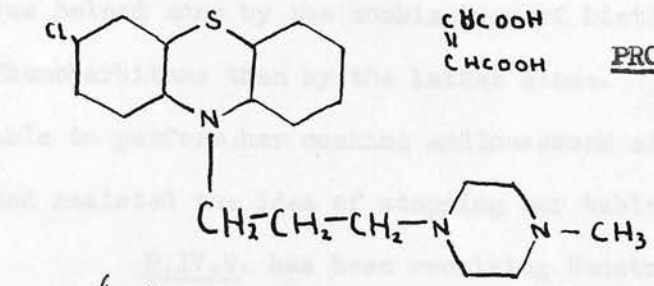
CHLORPROMAZINE HYDROCHLORIDE

2-chloro-10-(3-dimethylaminopropyl) phenothiazine Hydrochloride



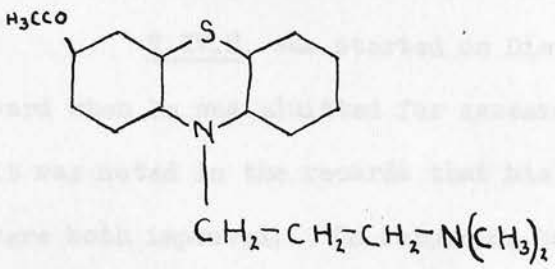
PROMAZINE HYDROCHLORIDE

10-(3-Dimethylaminopropyl) phenothiazine Hydrochloride



PROCHLORPERAZINE DIMALEATE

1-{3-(3-chloro-10-phenothiazinyl)-propyl}-4-methyl piperazine Dimaleate.



ACETYLPROMAZINE MALEATE

3-acetyl-10-(-3-dimethylaminopropyl) - phenothiazine Maleate.

In this series five patients were not at a stage suitable for treatment with these drugs. Benzhexol was given to five patients but no improvement could be credited to the drug. Dosage was adequate in each case being pushed to the limit of tolerance at about 20 mgm. daily. P.IV.5 was treated in turn with each drug in this group but there was no improvement demonstrated. As this patient died in 1956 it can safely be assumed that the disease had advanced too far and the cerebral damage was too widespread and permanent to expect any relief of her symptoms. This is confirmed by the details of her clinical history. P.IV.8 died the year before his sister and similar reasons can be extended as to why the Benzhexol did not help him.

A.II.5, the patient with non-hereditary chorea, was helped more by the combination of Diethazine and Phenobarbitone than by the latter alone. She was better able to perform her cooking and housework after treatment and resisted the idea of stopping her tablets.

P.IV.9. has been receiving Benztropine along with several other drugs. The ward attendants did feel that her Benztropine was helping her when it was started but now that dementia is evident the picture is less clear.

T.IV.8. was started on Diethazine in a medical ward when he was admitted for assessment. After two weeks it was noted in the records that his speech and his gait were both improved. On returning home his family also noticed that he was more mobile.

C.IV.13. received a month's course of Benzhexol without noticing any benefit. Some considerable time later she received a similar dose under a different proprietary name along with Phenobarbitone gr. $\frac{1}{2}$ t.i.d. The effect of this was better than that from Phenobarbitone alone. She was less depressed, showed less athetosis and was more mobile.

R.III.2. was treated with Diethazine, Benztropine and Benzhexol in separate courses but it is not clear why he was not improved.

N.III.27. received a trial of Benztropine only near the end of his life. The reason for the lack of response is obvious.

Promazine Compounds:- Seven patients have been treated with drugs of this group. All but one have had

Chlorpromazine but the dose has varied considerably from one patient to another. T.V.9 is the only patient to derive help from this substance. A few years ago it was found to help her depression but now as she lies in bed with advanced dementia it is employed in a dose of 50 mgm. t.i.d. to control her temper.

Two patients, N.III.27 and R.III.4 failed to respond to Prochlorperazine or Acetylpromazine but by the time these drugs were used the disease was very far advanced.

C.IV.13 improved a little with Prochlorperazine but after a few months she had a relapse in her chorea as the result of an attack of influenza and was then started on the new preparation of Benzhexol.

P.IV.9 was given Promazine for a few months when she was in a restless phase, this made her much more amenable to life in the ward and her attendants thought that there was a slight reduction in her athetosis.

The behaviour of C.IV.9 is very complicated and unsuitable for assessing the value of any drug. This patient could be classed as a high grade defective in addition to his Huntington's Chorea. Chlorpromazine has been prescribed for him but it is doubtful if in his present state of neglect he takes it.

In summarising the results achieved in this phase of medical treatment of Huntington's Chorea undue modesty should not be allowed to suppress the many signs of encouragement. Variation of the drugs and their dosage together with variation in the condition of the patients makes it difficult to show in hard facts a

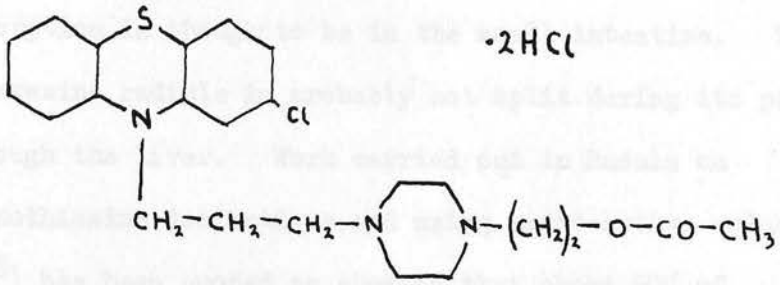
sufficiency of concrete evidence which will convey the true picture. That many of the patients have been in some way improved by Phenothiazine derivatives is not in doubt and several of the local practitioners have expressed relief that for the first time there are drugs available now which can bring a measure of relief to their patients. Thus the results of using Phenothiazine drugs in the treatment of Huntington's Chorea compared with the hopelessness of previous experience has encouraged a continuing search for a substance which will be effective.

CLINICAL TRIAL

Experience has shown that up to a decade ago drug therapy did not influence the symptoms of Huntington's Chorea but since Phenothiazines have become available there has been some encouraging signs of improvement. With the rapid expansion in this field of therapeutics over the last ten years it has been possible to keep hoping that some drug would be offered which would be of value in the treatment of Huntington's Chorea.

With the object of finding a substance of greater therapeutic potency than the drugs already available and yet without the major side effects, a new preparation was synthesised. This is:- 1-(2-acetoxyethyl)-4-{3-(2-chloro-10-phenothiazinyl) propyl} piperazine dihydrochloride. It was issued to us for experimental use under the code number SC-7105, later to be given the official name of Thiopropazate Dihydrochloride. The drug has a close structural relationship to Chlorpromazine.

CHEMISTRY:-



Structure of 1-(2-acetoxyethyl)4-{3-(2-chloro-10-phenothiazinyl) propyl} piperazine dihydrochloride.

This is a white crystalline powder and is readily soluble in water (36).

Toxicity:- Studies (36) on mice indicated a high therapeutic index and a high ratio of safety. The LD_{50} in these animals was determined to be 279 mgm. per kilogram of body weight when administered orally and 197 mgm. per kilgram when given parentrally.

Other groups of animals were observed over longer periods with both small and high dosage of the substance. Growth, body weight and appetite remained normal. Blood counts, electrolyte studies and tests of hepatic and renal function were unaltered.

Pharmacology:- In different animal experiments (36) separate responses were investigated, prevention of apomorphine emesis, occurrence of tranquillity, ataxia, pupillary miosis and relaxation of the nictitating membranes, hypotensive effects and the reduction of work performance were all tested. It was concluded that SC-7105 was about five times as potent as Chlorpromazine

and very much less toxic.

SC-7105 is effective when given by mouth. Absorption is thought to be in the small intestine. The piperazine radicle is probably not split during its passage through the liver. Work carried out in Russia on phenothiazine derivatives and using radio-active sulphur (S^{35}) has been quoted as showing that about 90% of Chlorpromazine was excreted in the stool and about 5% excreted in the urine.

Groups of patients with a variety of different psychoses have been treated with SC-7105 by Matthews (37) and by Hamilton (38).

A possible mode of action of SC-7105 will be discussed later.

Method:- Many local peculiarities made it possible to collect together only five cases of proved Huntington's Chorea. It was felt that patients should not be included whose condition had advanced beyond hope of improvement and on the other hand any suspected but unproved case would still have enough insight to learn what was afoot and the type of patients with whom they were being classified. The other case in the series was shown to be suffering from a non-hereditary chronic chorea.

In order to achieve a standard environment for the trials the patients were all treated at home. Past experience had shown that admission to hospital benefited the patient from the point of view of nutrition, clean-;liness and mood, and this appeared to improve the symptoms. Fortunately, during the trial, none of the patients suffered any infections which might have affected them

adversely.

Though the patients were specially examined before, during and after the trial, the local practitioners continued to pay the regular visits and provided the interim observations. This was felt to be the best arrangement as the patients were familiar with their doctors and these men were able to notice any changes, having fore-knowledge of the patient as well as many years experience of treating Huntington's Chorea.

In view of the small number of patients concerned it was not practical to follow the double blind technique. Instead the patients formed their own controls during the second phase of the trial which proved a useful way to even out the individual variations amongst the patients and avoid the majority of the pitfalls to be expected with uncontrolled observations.

The cases were treated with SC-7105 for a period of three months receiving one 10 mgm. tablet thrice daily after meals. The drug was then discontinued and for a second period of three months, tablets which were inert but of similar appearance were given as a control. The original drug was then administered once more, but in a totally different form, namely as a pink-sugar-coated tablet, instead of the original white tablet. All other drugs affecting the nervous system were stopped during this this time. Checks of blood, urine and blood pressure were carried out periodically along with frequent assessment of the patient's physical ability, mental state and the condition of the house.

Results:- There were many drawbacks to devising

a yardstick or a formula by which the patients' progress could be gauged collectively. It is considered more suitable to review each case individually.

The numbers by which each patient is designated refer to the foregoing commentary on Huntington's Chorea in Avoch. The geneology and the early history of each patient is to be found in that section.

Previous drug therapy is to be found surveyed above but for convenience it will be repeated when the patients are described as they were at the commencement of the trial.

C.IV.13. Aged 64.

This patient had exhibited a chorea for 12 years. Physically she was able to move about the house but was unable to dress herself and undertook no part in the housework but tended to spend much of her day sitting in an easy-chair often paying little interest to her surroundings. At times she was calm and willing to converse but on closer questioning the family admitted she was sometimes liable to be easily irritated and even had an occasional outburst.

During the examination there was some difficulty in concentrating for very long and this, combined with her athetosis, gave a false impression of poor-co-operation. Her athetoid movements were fairly continuous but neither very sudden nor very extensive. Her speech was thickened and slurred. Her head gave occasional small nods, the hands could remain on her lap but were continually working away in a purposeless fashion. In a similar way the feet had a continuous shake which she tried to hide by

crossing the legs. Occasionally her trunk gave a slight jerk. Muscle tone was to some extent increased. The reflexes were brisk but gave no indication of an upper motor neurone type of involvement.

The patient was interested in the procedure of examination and was at times over anxious to help but this was poorly sustained. She was well orientated but her memory was poor particularly for event in recent months. She gave no indication of excitement. The family stated that she was never concerned about her appearance or the care of her house. The amount of help which she required varied from time to time and seemed to be worse when she was irritable. Her husband, a retired sea-captain, attended to her immediate wants and her daughter who lived near-by ran the house.

At the time of her first examination therefore she had a mild chorea, commencing cerebral degeneration and a mild cyclical depression. The patient herself had no insight but the family were aware that a new tablet was being tried out.

Apart from sedatives this patient had been tried without result on Benzhexol, Chlorpromazine and Tolazoline.

Within two weeks of starting SC-7105 there was a marked diminution in her choreic movements and after a further two days they were barely perceptable. In parallel with this was some increase in spasticity so that any improvement in her walking was obscured by an increased stiffness. She showed more concern about her surroundings when she started the tablets and the family was greatly encouraged to see her face show a "more alive

look." When the stiffness became apparent she was not unnaturally somewhat depressed about it and tended to shut herself off from her surroundings again. She became silent and had an immobile expression. When this change was at its height she would sit where she had been put in a chair gazing in front of her. Movements were well controlled but slow and appeared to lack strength. She hardly ever initiated movements. Reflexes were brisk, being a little increased and the passive movements of limbs revealed some additional increase of muscle tone.

K.IV.32. Aged 64.

This man had a well established psychosis and a coarse and active chorea for three years. The psychosis was particularly manifested as a religious mania and he would spend considerable periods in the street preaching long an involved sermons to which no-one paid any attention or even listened. Along with this there was depression and he would swing easily from the depression to intensely excited and elated behaviour. He was well orientated but much of the poverty of memory, intellect and concentration had probably been present all his life. His chorea was very obvious and involved the whole body. The head jerked especially to the right and more so when speaking. Speech was difficult to understand because of the continual grimacing as well as uncontrolled movement of the tongue. Frequent jerks of the body while sitting made him look as if he had given a small jump. The arms and legs, always on the move, had very rapid and extensive jerks.

He co-operated well with the examination though he found the chorea interfering with some of the tests.

A slight increase in tone was noted along with some increased activity of the tendon reflexes.

In the house he was looked after by a very attentive wife who complained only about the times when he was too excited. For the examination he dressed and undressed himself, giving a good demonstration of the movements he had developed to overcome and conceal his chorea. His movements could be quick and well directed if he paused during a jerk and completed his action when he was again in control of his limbs. His walking was uneven. Fine movements were impossible and meal-time was apt to be a little trying.

Phenobarbitone had quietened him a little in the past. Mephenesin was also tried but without success.

It was about two weeks before the benefit of SC-7105 became apparent. The first improvement to be noted was that he became much calmer and, for the first time in twenty years, he agreed to give up his preaching. His family thought that he was much more settled in his mind.

Over a period of a few days the chorea diminished greatly and then almost ceased. His appetite improved and he slept more peacefully at nights. The reduction of the chorea helped to increase this patient's functional ability greatly. Besides appearing to find the tests easier to perform his movements were more accurate and stronger. Speech was only a little better because a thickness persisted. His walking was still erratic but much less so than before. He was able to dress and undress much more quickly and was much less flustered

while doing this. No increase of tone was noted in the limbs and in fact the movements appeared much more free.

When the first tablets were stopped his condition reverted rapidly to its former state except that he did not return to the preaching. Had it not happened that the supplies of the tablets in the country were exhausted it would have been impossible to continue the control period, so greatly impressed were his family with these tablets.

R.III.2. Aged 75.

A chronic bronchitis with asthma complicated the medical picture of Huntington's Chorea in this case. In addition to a true bronchial asthma with spasm this man has a rare feature of a periodically jerking type of respiration associated with his chorea.

Drugs which have been tried unsuccessfully in this case include the sedatives Phenobarbitone and Amylobarbitone as well as the newer Diethazine Hydro-:chloride, Chlorpromazine and Benztropine Methanesulphate.

This man has always been regarded as being simple. He is of poor intellectual capacity and generally he is placid. This feature had not increased over recent years to suggest that he has any marked progressive cerebral degeneration. He has never been sociable and has in fact led rather a lonely life and at times is apt to become somewhat depressed. His memory and orientation were good.

The athetosis was well marked and troublesome. It had appeared over eight years before. Head, facial expression and speech were only involved to a moderate degree. The gait was erratic and staggering. The

involuntary movements in his hands limited their usefulness as he had considerable difficulty with buttons though he could otherwise dress himself and look after most of his immediate requirements.

Examination showed a widespread chorea with slow movements of wide excursion but no increase of muscle tone. Emphysema, and the changes associated with chronic bronchitis and asthma, were found but no other significant changes were present.

Definite improvements were noted by the eleventh day after starting treatment with SC-7105. He was able to concentrate better, he slept better and appeared to be less depressed. He became more reliable on his legs. He gradually began to undertake jobs around the house as the chorea lessened in the arms and was eventually able to help the fishermen to mend their nets, a highly specialised operation which would have been quite impossible before.

With discontinuance of the drug he relapsed and in about five days the chorea was as marked as it had been before but the depression was scarcely so obvious. When SC-7105 was restarted, the improvement in his ability to work reappeared again.

The movements of his limbs lessened mostly in frequency but there was also some diminution in the range of the movement. No spasticity developed, on the contrary, the limbs appeared to move much more easily as they were very much better controlled.

N.III.27. Aged 74.

This man was difficult to look after at home. Previous treatment with Amylobarbitone 1 gr. t.i.d. had helped him for a spell some years before but had not made any difference to his chorea. Chlorpromazine had been given at a different time but failed to influence him.

The chorea had been present for about ten years and was very incapacitating. The whole body was involved in these continual purposeless movements which had the form of a writhing rather than a jerking. Dyslalia made his speech almost incomprehensible and this added a further frustration as he would have like to be a conversationalist. The head constantly nodded and he was always grimacing. The trunk was also involved. The function of his limbs was so affected that he had to be fed, washed and clothed. He could walk but with great uncertainty and it was more or less limited to moving him from one seat to another.

The patient had a determined and aggressive personality which became obvious as the examination proceeded. He kept interrupting to begin a conversation which if allowed to continue was turned by him into an argument and he became very excited. He was well orientated but had a restriction in his ability to concentrate and gaps in his memory.

Physical examination was hampered by an inability to co-operate and the chorea. A slight, generalised muscular weakness was noted but no spasticity was evident.

For a week there was no obvious change after starting to take SC-7105 but then over a period of a week the improvement was remarkable. He became less fiery in argument and then less liable to argue. His aggressiveness disappeared. He became more at peace and much less tense. Sleeping and appetite improved. The athetosis lessened considerably in severity so that he spoke with more freedom, his gait became steadier and his hand grip became stronger. After a short while he was able to feed himself and eventually he was able to eat a boiled egg by himself for the first time in ten years.

After the inert control tablets were introduced to replace the first drug, he deteriorated markedly and was back to his previous state within two days. He eventually went right off his feet, but on restarting SC-7105 he regained in two months the ground he had previously made.

K.V.2. Aged 38.

This lady is much younger and her symptoms milder than the other patients included in this trial. Signs of incipient Huntington's Chorea have been observed over the past seven years but her symptoms have not upset her. There was no trace of a frank psychosis but she had occasional long bouts of depression when the house and family were neglected and at these times her chorea was more marked. Phenobarbitone was the only drug which had been used previously with any success. During the year before this new preparation was introduced, the chorea was obvious but by no means continuous or even sustained. Her feet would give occasional jumps and she showed a

shuffling tendency in her walk, frequently tripping as she moved. For necessary housework her hands were still serviceable but fine work such as knitting and mending had been passed over to her mother. Heavy tasks and shopping were found to tire her unduly. She suffered from a generalised pruritus which did not resolve on symptomatic treatment. The head jerked but there was no grimacing nor difficulty with speech.

Examination confirmed this description and when holding a limb it was obvious that many more muscular contractions occurred than were betrayed by her movements. No other significant signs were noted. Memory and concentration were good. Within three weeks of starting SC-7105 there was considerable improvement, the itch was much less, the chorea had virtually disappeared and her general physical condition was very markedly improved. She was not put to the test of the family mending because her mother insisted on carrying on with it but her movements became more free as the chorea receded. She was much more cheerful and there was no trace of her tiredness.

She had previously performed her tests for the examination remarkably well though they were able to accentuate the chorea. When the examination was repeated she showed far fewer jerks to interrupt the free movement of her limbs and without previous knowledge of her case she might well have been passed as normal. The episodic nature of her symptoms caused worry lest a spell of spontaneous improvement might be mistaken for the result of therapy. No such confusion did in fact arise as the pattern corresponded so closely with the tablets she

received. When SC-7105 was stopped she regressed in three days and when they started again the benefit was noticed once more after three weeks.

A.II.5. Aged 58.

This lady's case has already been described on page 14. A diagnosis of non-hereditary chorea had been agreed but she has been included in the trial to test the specificity of the drug. After ten years of chorea she had learned to accommodate herself to it. Her trunk remained still, the feet moved continuously and the hands writhed perpetually in her lap. The head frequently jerked to the side and her speech showed she was not in full control of her tongue. While walking she reached for pieces of furniture, but could walk unsupported. The fine and complicated movements defeated her but she cooked and cared for the house after her fashion. Memory was well preserved and she could concentrate for reasonable spells.

After taking SC-7105 for four days she felt much calmer. Two weeks later her limbs became steadier and housework was appreciably easier. In the next ten days her chorea was much less obvious.

The change to inert tablets caused the return of her athetosis and after a week it was as obvious as it had been before. Meals were late and the house again began slowly to take on a neglected look. The patient herself became easily excited again and this also upset her work because she found she could not cope with the house so well as when she had been taking SC-7105. The

continual moving of her hands and feet and the jerking of her head reappeared, eventually assuming the proportions which it had previously.

On returning to SC-7105 the picture of improvement reappeared and she remained as well as she had been in the early part of the trial.

Toxic effects:- Frequent observations were made on these patients throughout the course of the trial but no adverse side effects were noted outside the nervous system. There was no evidence of haemopoetic, cardio-:vascular, renal or hepatic dysfunction in any of these patients.

The immobility of expression, slight increase in spasticity and depression encountered with patient C.IV.13 was a purely temporary phenomenon and did not require special treatment.

Progress:- To cover the interval since this trial began a brief progress note is appropriate.

One case has died. N.III.27 was up in years when SC-7105 produced such a remarkable improvement in his chorea but by this time the disease had made him frail and appear very old. He continued to be able to get up, dress himself and go for walks but herein lay his downfall. When his daughter left to go to Canada the responsibility and care of the patient proved too much for his elderly wife, particularly as he started wandering out of his gate on to a major main road. For his own care and protention he was admitted to Craig Dunain Hospital a year after the

trial as a case of senile dementia and died of broncho-:pneumonia six months later.

One patient has now discontinued the tablets. The mild temporary catatonic phase suffered by C.IV.13 so upset the emotions of her relatives that they would not allow the third phase of the trial to continue and though the beneficial effect of SC-7105 on her chorea had already been proved she is now maintained on ever-changing combinations of other phenothiazine drugs and Phenobarbitone. Even on this regime she is a little better than before the trial.

The drug was continued in the four remaining cases. R.III.2 has aged greatly in recent months. Besides the frailty of his years and the effects of his bronchitis and asthma there has also been an advancing cere-:bral deterioration. The patient's athetosis is very much less marked than previously and it is undoubtedly due to the SC-7105 and he keeps so well at present.

K.IV.32 progressed satisfactorily and has been able to get about, doing small jobs for the house which previously his chorea would have prevented. His mood, however, has varied and at times when he is irritable there has been some increase in the athtosis. On average, this man's improvement is well marked.

A.II.5 and K.V.2 continue to show a great benefit from their treatment. A greater degree of excitement is required to upset them now but when this occurs as it does very occasionally they both show a slight increase of

the chorea and some loss of physical ability. The chorea has not advanced appreciably in either and there have been no psychiatric developments. Both families and their relatives are very relieved by this treatment which all are anxious to continue.

Results:- Five patients with Huntington's Chorea and one with a non-hereditary form of chorea have each been benefited by treatment with SC-7105. The most immediate response which usually occurred on the 2-3rd day has been to temper their excitability and prevent the outbursts which were common before.

A very remarkable improvement in the chorea has been noted in each case, usually starting about 2-3 weeks after taking the tablets. Using as a guide to assess progress, the patient's ability to perform every day tasks, each case has improved to a degree varying proportionally to the incapacity at the outset. Thus the pair most affected, N.III.27 and R.III.2, showed the most spectacular improve-:ment. The first returned to managing a boiled egg himself after being unable to do so for ten years. The second recovered the not inconsiderable skill of being able to mend fishing nets.

The pair, C.IV.13 and K.IV.32, are placed roughly midway in that their ability improved from being able to care for themselves, to being capable of useful tasks round the house.

K.V.2 and A.II.5 were the mildest cases and had the least improvement to demonstrate. Both did, however, manage to show more efficiency in their houses. They are now virtually free from chorea.

Psychiatric disturbance was diminished in the two cases in whom it was marked before. N.III.27 changed from being very aggressive and quarrelsome into a quiet old man while K.IV.32 forsook his religious rantings.

The manic-depressive tendency which was marked with K.IV.32 but less obvious with A.II.5, C.IV.13 and K.V.2 has been considerably lessened.

Intellectual powers of the patients in whom it had been limited have improved. Thus the three men each showed a greater interest in activities around them and became interested again in the daily newspapers which they had not touched for years.

The dementia alone has not responded to this form of treatment. In R.III.2 this has now become obvious where it could only be suspected before. N.III.27 became more active than was safe for his degenerate brain and he had to be admitted to hospital for care and his own safety.

One case, C.IV.13, showed a temporary and minor pseudo-Parkinson state but otherwise no untoward side effects of SC-7105 were encountered.

Discussion:- The symptoms of Huntington's Chorea can be grouped under the headings of progressive dementia, athetosis and usually a psychosis. A great step forward can be claimed in the introduction of SC-7105 which has now been shown to influence the chorea and psychosis though the action on the dementia is less certain.

Barbiturate sedation was previously the only effective treatment for Huntington's Chorea but this was extremely limited in its results. When phenothiazine drugs

began to be used they did help a little more but the response to them was very erratic and usually disappointing.

The choice of patients for this trial has been limited by local conditions and one case of a non-hereditary chronic chorea has been added. These patients fall roughly into classes of differing age and type. Two cases were young and mildly affected. At the other extreme were two men who, though they had advanced disease, were judged to be still capable of improvement. The remaining pair were cases of middle-age and of moderate severity.

The results have shown a remarkable improvement in the athetosis and the mental symptoms and this has been interpreted in terms of an increase of activity and usefulness of the patient.

The initial improvement was in the composure of the patient and could have been anticipated from the known "tranquillizing" effect which has been found with drugs of the promazine type. This occurred within 2-3 days of commencing treatment and has suggested the mechanism of sedation, possibly with a purely chemical action.

About three weeks after starting to take SC-7105 the chorea was first noticed to be lessening and it continued to diminish over the next few days. This longer delay may suggest a replacement mechanism, blockage of enzymes or depletion of a body store.

It might be argued that many patients notice that they are worse when they are excited and that many other factors will influence the activity of their athetosis. Some improvement has been demonstrated in these cases when

they are calmed by barbiturates but the great improvement in physical condition quoted above outweighs by far the benefit obtained from sedation as had been observed previously in each of these patients. It is therefore claimed that SC-7105 has a much more specific action than being a general sedative.

The dementia alone has not been helped apparently. In retrospect this degenerative process was probably already established and beginning to progress in the two elderly men and it may be considered unfair to expect a drug to halt such a process once begun. It will take many more years of observation to show whether SC-7105 will prevent or delay the dementia in the younger patients who are at present clear. These future observations should help to decide whether SC-7105 is striking at the disease itself or is merely dempening down the symptoms while the disease progresses. From this will also come the answer as to the liekly use of giving SC-7105 prophylactically to suspected and pre-Huntingtonian patients.

The correct dose of SC-7105 which has to be given may also be deduced from this trial. 30 mgm. a day was given to all the patients in this series and as they all improved so dramatically this may be assumed to be an effective dose.

The pseudo-Parkinsonism which was exhibited by C.IV.13 can be taken as a sign of over-dosage and this can be explained by reason of her small size. None of the other patients who were of average weight and height showed any side effect with 30 mgm. daily whereas this patient was

petite and might have been helped adequately with 20 mgm. daily without developing side effects.

A reaction of this type has already been known with other drugs of this group and in a discussion of this subject Kruse (40) relates its occurrence to the size of the dose explaining that it is probably simply a feature of over-dosage and one disadvantage in having more potent drugs. This information is of great value in attempting to explain the action of this group of substances.

Perdon Martin (41) has very recently reviewed our rather imperfect understanding of the function of the basal ganglia particularly as they are concerned with postural fixation. He claims that in hemiballismus the "muscular mechanism responsible for fixation of the limbs and trunk is acting wildly." "Further, a lesion in the pallidum ... abolishes the involuntary movements and the patient can then move the previously affected limbs normally."

If this is illustrated in the most elementary terms and applied to the problem in hand a simplified working hypothesis can be devised.

Condition	Site of Lesion	Result
Paralysis Agitans	Substantia Nigra	Spasticity
Huntington's Chorea	Caudate and Putamen	Athetosis

At least two types of regulating mechanisms are exerted on voluntary movement by the basal ganglia and these normally form a harmonious balance. If from any reason the influence of one regulator is lost, the other acts without

restriction and locomotion is disordered. Should it be possible, however, to find a sedative, sufficiently selective to depress the action of this over-acting mechanism, then some of the disharmony in voluntary movement may be removed.

It is suggested that when atrophy of the caudate and putamen occurs as in Huntington's Chorea the unopposed actions of the unaffected area are responsible for the athetosis. When these areas are subdued by SC-7105 some alleviation of the symptoms may be expected. If, however, these unaffected areas are excessivly suppressed by an overdose of SC-7105 and the caudate is only partially atrophic, then the opposite syndrome occurs, namely pseudo-Parkinsonism.

The full variety of actions which phenothiazine substances will produce in the body has not yet been clarified but one of their known effects is to depress cellular activity in all types of living organisms. Decourt (42) illustrated this experimentally and claimed that it acts on brain tissue where there are numerous synapses.

Amongst work in progress at present is research at cell level which shows that these drugs act on enzymes of the respiratory chain. Dawkins (43) has demonstrated the action of some phenothiazine derivatives in inhibiting the enzymes cytochrome oxidase and D.P.N.A. - cytochrome - C reductase.

It can be readily imagined therefore that by selectively depressing the nerve cells of the undamaged regulatory mechanisms in the basal ganglia, SC-7105 brings

tranquillity to the patient suffering from Huntington's Chorea.

Conclusions:- 1-(2-acetoxyethyl)-4{3-(2-chloro-10-phenothiazinyl) propyl} piperazine dihydrochloride is a highly effective and very safe substance for the treatment of the athetosis and psychosis of Huntington's Chorea. The results have compared very favourably with previous forms of treatment, including other derivatives of phenothiazine.

The trial was conducted in the environment of home care and lasted nine months.

Good results have been obtained in the series of six cases of chronic chorea. Five were familial, one was non-hereditary.

Apart from a temporary disturbance in one patient due to overdosage no toxic effects were noted.

An attempt has been made to explain the mechanism of the drug's action.

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